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(71) Applicant *(for all designated States except US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **EICKMEIER, Christian** [DE/DE]; Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **DOERNER-CIOSSEK, Cornelia** [DE/DE]; Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **FIEGEN, Dennis** [DE/DE]; Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **FOX, Thomas** [DE/DE]; Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **FUCHS, Klaus** [DE/DE]; Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **GIOVANNINI, Riccardo** [IT/IT]; Boehringer Ingelheim Italia S.p.A., Via Lorenzini 8, I-20139 Mailand (IT). **HEINE, Niklas** [DE/DE]; Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **HENDRIX, Martin** [DE/US]; 12 Del Mar Court, Orinda, California 94563 (US). **ROSENBROCK, Holger** [DE/DE]; Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **SCHAENZLE, Gerhard** [DE/DE]; Boehringer Ingelheim GmbH, CD Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(74) Agents: **HAMMANN, ET.AL., Heinz** et al.; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

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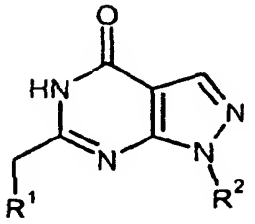
(54) Title: 1, 5-DIHYDRO-PYRAZOLO (3, 4-D) PYRIMIDIN-4-ONE DERIVATIVES AND THEIR USE AS PDE9A MODULATORS FOR THE TEATMENT OF CNS DISORDERS



(I),

(57) Abstract: The invention relates to novel substituted pyrazolopyrimidines. Chemically, the compounds are characterised by general Formula (I): with R^1 being phenyl or pyridyl, any of which is substituted with 1 to 4, preferably 1 to 3 substituents X; X independently of each other being selected from C_2-C_6-alky$_1$ or Ci-C_6-alkoxy, where C_2-C_6-alkyl and C_1-C_6-alkoxy are at least dihalogenated up to perhalogenated. preferably with 2 to 6 halogen substituents, and the halogen atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro; R^2 being phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyI, C_1-C_6-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6- alkylamino, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1- C_6-alkylaminocarbonyl. C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl. heteroarylcarbonylamino, C_1-C_6-alkylsulphonyl- amino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio; The new compounds shall be used for the manufacture of medicaments, in particular medicaments for improving, perception, concentration, learning and/or memory in patients in need thereof.

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1,5-DIHYDRO-PYRAZOLO[3,4-D]PYRIMIDIN-4-ONE DERIVATIVES AND THEIR USE AS PDE9A MODULATORS FOR THE TREATMENT OF CNS DISORDERS

The invention relates to novel substituted pyrazolopyrimidines. The new compounds shall be used for the manufacture of medicaments, in particular medicaments for improving perception, concentration, learning and/or memory in patients in need thereof. E.g. for the prophylaxis and treatment of Alzheimer Disease.

Chemically, the compounds are characterised as 6-aryl- or heteroarylmethyl-substituted pyrazolopyrimidines (more specific 6-benzyl or pyridyl-methyl-pyrazolopyrimidinones) having at least one alkyl or alkoxy residue at the aryl or heteroaryl moiety which in addition may be several fold substituted. Further aspects of the present invention refer to a process for the manufacture of the compounds and their use for producing medicaments.

BACKGROUND OF THE INVENTION

The inhibition of phosphodiesterase 9A (PDE9A) is one of the current concepts to find new access paths to the treatment of cognitive impairments due to CNS disorders like Alzheimer's Disease. With the present invention, new compounds are presented that follow this concept.

Phosphodiesterase 9A is one member of the wide family of phosphordiesterases. These kinds of enzymes modulate the levels of the cyclic nucleotides 5'-3' cyclic adenosine monophosphate (cAMP) and 5'-3' cyclic guanosine monophosphate (cGMP). These cyclic nucleotides (cAMP and cGMP) are important second messengers and therefore play a central role in cellular signal transduction cascades. Each of them reactivates inter alia, but not exclusively, protein kinases. The protein kinase activated by cAMP is called protein kinase A (PKA), and the protein kinase activated by cGMP is called protein kinase G (PKG). Activated PKA and PKG are able in turn to phosphorylate a number of cellular effector proteins (e.g. ion channels, G-protein-coupled receptors, structural proteins, transcription factors). It is possible in this way for the second messengers cAMP and cGMP to control a wide variety of physiological processes in a wide variety of organs. However, the cyclic nucleotides are also able to act directly on effector molecules. Thus, it is known, for example, that

cGMP is able to act directly on ion channels and thus is able to influence the cellular ion concentration (review in: Wei *et al.*, *Prog. Neurobiol.*, **1998**, *56*, 37-64). The phosphodiesterases (PDE) are a control mechanism for controlling the activity of cAMP and cGMP and thus in turn for these physiological processes. PDEs hydrolyse the cyclic monophosphates to the inactive monophosphates AMP and GMP. Currently, 11 PDE families have been defined on the basis of the sequence homology of the corresponding genes. Individual PDE genes within a family are differentiated by letters (e.g. PDE1A and PDE1B). If different splice variants within a gene also occur, this is then indicated by an additional numbering after the letters (e.g. PDE1A1).

Human PDE9A was cloned and sequenced in 1998. The amino acid identity with other PDEs does not exceed 34% (PDE8A) and is never less than 28% (PDE5A). With a Michaelis-Menten constant (Km) of 170 nM, PDE9A has high affinity for cGMP. In addition, PDE9A is selective for cGMP (Km for cAMP=230 [mu]M). PDE9A has no cGMP binding domain, suggesting that the enzyme activity is not regulated by cGMP. It was shown in a Western blot analysis that PDE9A is expressed in humans inter alia in testes, brain, small intestine, skeletal muscle, heart, lung, thymus and spleen. The highest expression was found in the brain, small intestine, kidney, prostate, colon, and spleen (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564; Wang *et al.*, *Gene*, **2003**, *314*, 15-27). The gene for human PDE9A is located on chromosome 21q22.3 and comprises 21 exons. To date, 4 alternative splice variants of PDE9A have been identified (Guipponi *et al.*, *Hum. Genet.*, **1998**, *103*, 386-392). Classical PDE inhibitors do not inhibit human PDE9A. Thus, IBMX, dipyridamole, SKF94120, rolipram and vinpocetine show no inhibition on the isolated enzyme in concentrations of up to 100 [mu]M. An IC50 of 35 [mu]M has been demonstrated for zaprinast (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564).

Murine PDE9A was cloned and sequenced in 1998 by Soderling *et al.* (*J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). This has, like the human form, high affinity for cGMP with a Km of 70 nM. Particularly high expression was found in the mouse

kidney, brain, lung and liver. Murine PDE9A is not inhibited by IBMX in concentrations below 200 [mu]M either; the IC50 for zaprinast is 29 [mu]M (Soderling *et al.*, *J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). It has been found that PDE9A is strongly expressed in some regions of the rat brain. These include olfactory bulb, hippocampus, cortex, basal ganglia and basal forebrain (Andreeva *et al.*, *J. Neurosci.*, **2001**, *21* (22), 9068-9076). The hippocampus, cortex and basal forebrain in particular play an important role in learning and memory processes.
As already mentioned above, PDE9A is distinguished by having particularly high affinity for cGMP. PDE9A is therefore active even at low physiological concentrations, in contrast to PDE2A (Km=10 [mu]M; Martins *et al.*, *J. Biol. Chem.*, **1982**, *257*, 1973-1979), PDE5A (Km=4 [mu]M; Francis *et al.*, *J. Biol. Chem.*, **1980**, *255*, 620-626), PDE6A (Km=17 [mu]M; Gillespie and Beavo, *J. Biol. Chem.*, **1988**, *263* (17), 8133-8141) and PDE11A (Km=0.52 [mu]M; Fawcett *et al.*, *Proc. Nat. Acad. Sci.*, **2000**, *97* (7), 3702-3707). In contrast to PDE2A (Murashima *et al.*, *Biochemistry*, **1990**, *29*, 5285-5292), the catalytic activity of PDE9A is not increased by cGMP because it has no GAF domain (cGMP-binding domain via which the PDE activity is allosterically increased) (Beavo *et al.*, *Current Opinion in Cell Biology*, **2000**, *12*, 174-179). PDE9A inhibitors may therefore lead to an increase in the baseline cGMP concentration.

WO 98/40384 discloses pyrazolopyrimidines which are PDE1, 2 and 5 inhibitors and can be employed for the treatment of cardiovascular and cerebrovascular disorders and disorders of the urogenital system.

CH 396 924, CH 396 925, CH 396 926, CH 396 927, DE 1 147 234, DE 1 149 013, GB 937,726 describe pyrazolopyrimidines which have a coronary-dilating effect and which can be employed for the treatment of disturbances of myocardial blood flow.

U.S. Pat. No. 3,732,225 describes pyrazolopyrimidines which have an antiinflammatory and blood glucose-lowering effect.

DE 2 408 906 describes styrylpyrazolopyrimidines which can be employed as antimicrobial and antiinflammatory agents for the treatment of, for example, oedema.

WO04099210 discloses novel 6-arylmethyl-substituted pyrazolopyrimidines which lack having at least one alkyl or alkoxy residue at the aryl moiety which is several fold substituted by halogen.

ASPECTS OF THE INVENTION

It is an aspect of the present invention to provide compounds that effectively modulate PDE9A for the purpose of the development of a medicament, in particular in view of diseases, the treatment of which is accessible via PDE9A modulation.

It is another aspect of the present invention to provide compounds that are useful for the manufacture of a medicament for the treatment of CNS disorders.

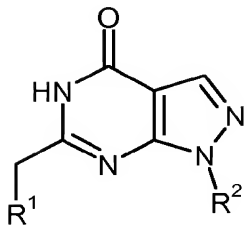
It is an aspect of one embodiment of the present invention to provide compounds which show a good safety profile.

Accordingly, it will be understood that another objective of the present invention is to provide compounds that inhibit PDE9A in a selective manner.

Yet another objective is to provide such a medicament not only for treatment but also for prevention or modification of the corresponding disease.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The compounds of the present invention are characterised by general formula I:



(I),

with:

R^1: the following substitution options **$R^{1.i}$** for **R^1** in the order of preference, ascending from preferably to most preferably are defined:

$R^{1.1}$: **R^1** being phenyl or pyridyl, preferably phenyl, any of which is substituted with 1 to 4, preferably 1 to 3 substituents independently selected from **X**,

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6-alkylamino, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by 1 to 3 radicals independently of one another selected from the group of hydroxy, cyano, halogen, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

with **X** (- independently of each other in case of more than one **X** -) being C_2-C_6-alkyl or C_1-C_6-alkoxy; each of which are at least dihalogenated up to perhalogenated and the halogen atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro. Preferred are substitution patterns in that at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferred at least

twofold halogenated. The beta position is the position next to the O-atom in case of C_1-C_6-alkoxy and in case of C_2-C_6-alkyl the C-atom next to the C-atom that is linked to the phenyl or pyridyl. For each embodiment of the present invention X preferably is C_1-alkyl-O or C_2-alkyl substituted as defined hereinbefore.

Preferably at least one **X** is in the ortho position to the C-atom of the phenyl-ring, the pyridylring respectively by which $\mathbf{R^1}$ is attached to the methylene group which links $\mathbf{R^1}$ with the pyrazolopyrimidine group of the of formula I.

$\mathbf{R^{1.2}}$: $\mathbf{R^1}$ being phenyl or pyridyl, preferably phenyl, any of which is substituted with 1 to 4, preferably 1 to 3 substituents independently selected from **X**, where **X** is substituted by at least 2, preferably 2 to 6 halogen atoms, selected from the group of fluoro, chloro and bromo, preferably fluoro substitutents

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, cyano, trifluoromethyl, nitro, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by 1 to 3 radicals independently of one another selected from the group of hydroxy, cyano, halogen, and a group of the formula $-NR^3R^4$,

with **X** (- independently of each other in case of more than one **X** -) being C_2-C_6-alkyl or C_1-C_6-alkoxy; each of which are at least dihalogenated up to perhalogenated and the halogen atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro. Preferred are substitution patterns in that at least the C-atom which constitutes the beta position with respect to

the link to the phenyl or pyridyl is at least one fold or more preferred at least twofold halogenated. The beta position is the position next to the O-atom in case of C_1-C_6-alkoxy and in case of C_2-C_6-alkyl the C-atom next to the C-atom that is linked to the phenyl or pyridyl. For each embodiment of the present invention **X** preferably is C_1-alkyl-O or C_2-alkyl substituted as defined hereinbefore.

Preferably at least one **X** is in the ortho position to the C-atom of the phenyl-ring or the pyridylring respectively by which $\mathbf{R^1}$ is attached to the methylene group which links $\mathbf{R^1}$ with the pyrazolopyrimidine group of the of formula I.

$\mathbf{R^{1.3}}$: $\mathbf{R^1}$ being phenyl or pyridyl, preferably phenyl, any of which is substituted with 1 to 4, preferably 1 to 3 substituents independently selected from **X**, where **X** is substituted by at least 2, preferably 2 to 6 halogen atoms, selected from the group of fluoro, chloro and bromo, preferably fluoro substitutents

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, trifluoromethyl, halogen,

with **X** (- independently of each other in case of more than one **X** -) being C_2-C_6-alkyl or C_1-C_6-alkoxy; each of which are at least dihalogenated up to perhalogenated and the halogen atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro. Preferred are substitution patterns in that at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferred at least twofold halogenated. The beta position is the position next to the O-atom in case of C_1-C_6-alkoxy and in case of C_2-C_6-alkyl the C-atom next to the C-atom that is linked to the phenyl or pyridyl. For each embodiment of the present invention **X** preferably is C_1-alkyl-O or C_2-alkyl substituted as defined hereinbefore.

Preferably at least one **X** is in the ortho position to the C-atom of the phenyl-ring or the pyridylring respectively by which $\mathbf{R^1}$ is attached to the methylene group which links R1 with the pyrazolopyrimidine group of the of formula I.

In another embodiment of the invention, $\mathbf{R^1}$ being $\mathbf{R^{1.i.a}}$ with i as being defined above (i.e. for $\mathbf{R^{1.i}}$ = $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$):

$\mathbf{R^{1.1.a}}$: $\mathbf{R^1}$ being $\mathbf{R^{1.1}}$ with **X** being C_2-C_6-alkyl; more preferably C_2-alkyl, being substituted by at least 2 halogen atoms, being selected from the group of fluoro, chloro and bromo, preferably fluoro. Preferably the beta position to the link between **X** and phenyl or pyridyl is at least twofold substituted, the term beta position is as defined for the same context under $\mathbf{R^{1.1}}$;

$\mathbf{R^{1.2.a}}$: $\mathbf{R^1}$ being $\mathbf{R^{1.2}}$ with **X** being C_2-C_6-alkyl; more preferably C_2-alkyl, being substituted by at least 2 halogen atoms, being selected from the group of fluoro, chloro and bromo, preferably fluoro. Preferably the beta position to the link between **X** and phenyl or pyridyl is at least twofold substituted;

$\mathbf{R^{1.3.a}}$: $\mathbf{R^1}$ being $\mathbf{R^{1.3}}$ with **X** being C_2-C_6-alkyl; more preferably C_2-alkyl, being substituted by at least 2 halogen atoms, being selected from the group of fluoro, chloro and bromo, preferably fluoro. Preferably the beta position to the link between **X** and phenyl or pyridyl is at least twofold substituted;

Preferably in any of the embodiments $\mathbf{R^{1.1.a}}$, $\mathbf{R^{1.2.a}}$, $\mathbf{R^{1.3.a}}$ at least one **X** is in the ortho position to the C-atom of the phenyl-ring or the pyridylring respectively by which $\mathbf{R^1}$ is attached to the methylene group which links R1 with the pyrazolopyrimidine group of the of formula I.

In another embodiment of the invention, $\mathbf{R^1}$ being $\mathbf{R^{1.i.b}}$ with i as being defined above (i.e. for $\mathbf{R^{1.i}}$ = $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$):

$\mathbf{R^{1.1.b}}$: $\mathbf{R^1}$ being $\mathbf{R^{1.1}}$ with **X** being C_1-C_6-alkoxy; more preferably C_1-alkoxy, being substituted by at least 2 halogen atoms, being selected from the group of

fluoro, chloro and bromo, preferably fluoro. Preferably the beta position to the link between **X** and phenyl or pyridyl is at least twofold substituted;

$R^{1.2.b}$: **R^1** being **$R^{1.2}$** with **X** being C_1-C_6-alkoxy; more preferably C_1-alkoxy, being substituted by at least 2 halogen atoms, being selected from the group of fluoro, chloro and bromo, preferably fluoro. Preferably the beta position to the link between **X** and phenyl or pyridyl is at least twofold substituted;

$R^{1.3.b}$: **R^1** being **$R^{1.3}$** with **X** being C_1-C_6-alkoxy; more preferably C_1-alkoxy, being substituted by at least 2 halogen atoms, being selected from the group of fluoro, chloro and bromo, preferably fluoro. Preferably the beta position to the link between **X** and phenyl or pyridyl is at least twofold substituted;

$R^{1.4.b}$: **R^1** being phenyl or pyridyl, preferably phenyl, any of which is substituted with 1 to 3 **X** being C_1-C_6-alkoxy, substituted by at least 2, preferably 2 to 6 halogen atoms, selected from the group of fluoro, chloro and bromo, preferably fluoro substitutents, whereby at least twofold halogenation at the position next to the O-atom is preferred,

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, trifluoromethyl, halogen,

$R^{1.5.b}$: **R^1** being 2-trifluoromethoxyphen-1-yl.

Preferably in any of the embodiments **$R^{1.1.b}$**, **$R^{1.2.b}$**, **$R^{1.3.b}$**, **$R^{1.4.b}$** at least one **X** is in the ortho position to the C-atom of the phenyl-ring, the pyridylring respectively by which **R^1** is attached to the methylene group which links **R^1** with the pyrazolopyrimidine group of the of formula I.

For all substitution patterns **$R^{1.1}$**, **$R^{1.2}$**, **$R^{1.3}$**, **$R^{1.1.a}$**, **$R^{1.2.a}$**, **$R^{1.3.a}$**, **$R^{1.1.b}$**, **$R^{1.2.b}$**, **$R^{1.3.b}$**, **$R^{1.4.b}$** the preferred substitution pattern at the 1 to 3 mandatory substituents **X** being C_2-C_6-alkyl or C_1-C_6-alkoxy respectively, whatever is appropriate, preferably are at

least 2, more preferably 3 fluoro substituents. The preferred position for these halogen substituents are the alpha or the beta position, more preferably at least the beta position of the C_2-C_6-alkyl residue or the beta position of the C_1-C_6-alkoxy residue, more preferably only the beta position. Whenever **X** is C_1-C_6-alkoxy trifluoromethoxy is preferred. Whenever **X** is C_2-C_6-alkyl 2,2,2-trifluoreth-1-yl or 1,2,2,2-tetrafluoreth-1-yl or 1,1,2,2,2-pentafluoreth-1-yl is preferred, more preferred 2,2,2-trifluoreth-1-yl.

For the embodiments with $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$, $\mathbf{R^{1.1.b}}$, $\mathbf{R^{1.2.b}}$, $\mathbf{R^{1.3.b}}$, $\mathbf{R^{1.4.b}}$ most preferred **X** is 1 substituent being trifluoromethoxy.

For the embodiments with $\mathbf{R^{1.1.a}}$, $\mathbf{R^{1.2.a}}$, $\mathbf{R^{1.3.a}}$ most preferred **X** is 1 substituent being 2,2,2-trifluoreth-1-yl or 1,2,2,2-tetrafluoreth-1-yl or 1,1,2,2,2-pentafluoreth-1-yl 2,2,2-trifluoreth-1-yl.

In all options for $\mathbf{R^1}$ ($\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$, $\mathbf{R^{1.1.a}}$, $\mathbf{R^{1.2.a}}$, $\mathbf{R^{1.3.a}}$, $\mathbf{R^{1.1.b}}$, $\mathbf{R^{1.2.b}}$, $\mathbf{R^{1.3.b}}$ $\mathbf{R^{1.4.b}}$) phenyl is preferred over pyridyl, with the substitution pattern as outlined above.

In all options for $\mathbf{R^1}$ defined by $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$, $\mathbf{R^{1.1.a}}$, $\mathbf{R^{1.2.a}}$, $\mathbf{R^{1.3.a}}$, $\mathbf{R^{1.1.b}}$, $\mathbf{R^{1.2.b}}$, $\mathbf{R^{1.3.b}}$ $\mathbf{R^{1.4.b}}$ at least one **X** preferably is in the ortho position to the C-atom of the phenyl-ring or the pyridylring respectively by which $\mathbf{R^1}$ is attached to the methylene group which links $\mathbf{R^1}$ with the pyrazolopyrimidine group of the of formula I. For the embodiment $\mathbf{R^{1.5.b}}$ **X** is trifluoromethyl in ortho position of the phenyl. As outlined in the definition of the embodiments for $\mathbf{R^1}$ defined by $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$, $\mathbf{R^{1.1.a}}$, $\mathbf{R^{1.2.a}}$, $\mathbf{R^{1.3.a}}$, $\mathbf{R^{1.1.b}}$, $\mathbf{R^{1.2.b}}$, $\mathbf{R^{1.3.b}}$, $\mathbf{R^{1.4.b}}$ **X** can be present 1, 2, 3 or 4 times. Preferably **X** is present 1, 2 or 3 times, more preferably 1 or 2 times, more preferably 1 time.

In all options for $\mathbf{R^1}$ defined by $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$ **X** being C_1-C_6-alkoxy is preferred over **X** being C_2-C_6-alkyl. Accordingly, any of the options $\mathbf{R^{1.i.b}}$ is preferred over any options of $\mathbf{R^{1.i.a}}$.

R^2: the following substitution options **$R^{2.j}$** for **R^2** in the order of preference, ascending from preferably to most preferably are defined:

$R^{2.1}$ **R^2** being phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6-alkylamino, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

$R^{2.2}$ **R^2** being phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6-alkylamino, halogen, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, and a group of the formula NR^3R^4,

In another embodiment $R^{2.2.a}$ R^2 is defined as for $R^{2.2}$ but without hydroxycarbonyl.

$R^{2.3}$ R^2 being phenyl or pyridyl, preferably phenyl or 3-pyridyl, where phenyl is substituted by 1 to 3 radicals and pyridyl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, trifluoromethyl, halogen and C_1-C_6-alkylthio,

where C_1-C_6-alkyl, C_1-C_6-alkoxy and C_1-C_6-alkylthio, are optionally substituted by one to three halogen radicals,

For all substitution patterns according to $R^{2.1}$, $R^{2.2}$, $R^{2.3}$ the preferred substitution pattern at phenyl and heteroaryl is one or two radical(s). Heteroaryl preferably is pyridyl (2-, 3-, 4-pyridyl) optionally having one or two radical(s).

For all substitution patterns according to $R^{2.1}$, $R^{2.2}$, $R^{2.3}$ the preferred heteroaryl is pyridyl, more preferably 3-pyridyl.

R^3: R^3 having the following substitution option $R^{3.1}$:

$R^{3.1}$ R^3 being hydrogen or C_1-C_6-alkyl,

R^4: R^4 having the following substitution option $R^{4.1}$:

$R^{4.1}$ R^4 being hydrogen or C_1-C_6-alkyl,

or

R^3 and R^4 together with the nitrogen atom to which they are bonded are defined as (abbreviation for this kind of definition = R^{3+4}, specifically $R^{3+4.1}$):

$R^{3+4.1}$: R^3 and R^4 together with the nitrogen atom to which they are bonded are 5- to 8-membered heterocyclyl.

Each of the letters or indexes i, j respectively in $R^{1.i}$ and $R^{2.j}$ is an index standing for 1, 2, 3, etc.

Specific embodiments according to the present invention are represented by each element of the following matrix I, matrix II and matrix III. The present invention includes each embodiment of matrix I, matrix II and matrix III, more preferably each embodiment of matrix II and matrix III and more preferably each embodiment of matrix III. The preference of the embodiments for each matrix ascends from the first line to the last line. This means that the embodiment, which is presented by the matrix III, last row (i.e. ($R^{1.5.b}$ $R^{2.3}$)) is the most preferred embodiment.

Each matrix is represented by two columns, one providing the number for an embodiment of the present invention and the other one describing said embodiment.

matrix I:

No.	embodiment
I-1	$R^{1.1}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
I-2	$R^{1.1}$ $R^{2.1}$ $R^{3+4.1}$
I-3	$R^{1.1}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
I-4	$R^{1.1}$ $R^{2.2}$ $R^{3+4.1}$
I-5	$R^{1.1}$ $R^{2.3}$ $R^{3.1}$ $R^{4.1}$
I-6	$R^{1.1}$ $R^{2.3}$ $R^{3+4.1}$
I-7	$R^{1.2}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
I-8	$R^{1.2}$ $R^{2.1}$ $R^{3+4.1}$
I-9	$R^{1.2}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
I-10	$R^{1.2}$ $R^{2.2}$ $R^{3+4.1}$
I-11	$R^{1.2}$ $R^{2.3}$ $R^{3.1}$ $R^{4.1}$
I-12	$R^{1.2}$ $R^{2.3}$ $R^{3+4.1}$
I-13	$R^{1.3}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
I-14	$R^{1.3}$ $R^{2.1}$ $R^{3+4.1}$
I-15	$R^{1.3}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
I-16	$R^{1.3}$ $R^{2.2}$ $R^{3+4.1}$
I-17	$R^{1.3}$ $R^{2.3}$

matrix II:

No.	embodiment
II-1	$R^{1.1.a}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
II-2	$R^{1.1.a}$ $R^{2.1}$ $R^{3+4.1}$
II-3	$R^{1.1.a}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
II-4	$R^{1.1.a}$ $R^{2.2}$ $R^{3+4.1}$
II-5	$R^{1.1.a}$ $R^{2.3}$ $R^{3.1}$ $R^{4.1}$
II-6	$R^{1.1.a}$ $R^{2.3}$ $R^{3+4.1}$
II-7	$R^{1.2.a}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
II-8	$R^{1.2.a}$ $R^{2.1}$ $R^{3+4.1}$
II-9	$R^{1.2.a}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
II-10	$R^{1.2.a}$ $R^{2.2}$ $R^{3+4.1}$
II-11	$R^{1.2.a}$ $R^{2.3}$ $R^{3.1}$ $R^{4.1}$
II-12	$R^{1.2.a}$ $R^{2.3}$ $R^{3+4.1}$
II-13	$R^{1.3.a}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
II-14	$R^{1.3.a}$ $R^{2.1}$ $R^{3+4.1}$
II-15	$R^{1.3.a}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
II-16	$R^{1.3.a}$ $R^{2.2}$ $R^{3+4.1}$
II-17	$R^{1.3.a}$ $R^{2.3}$

matrix III

No.	embodiment
III-1	$R^{1.1.b}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
III-2	$R^{1.1.b}$ $R^{2.1}$ $R^{3+4.1}$
III-3	$R^{1.1.b}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
III-4	$R^{1.1.b}$ $R^{2.2}$ $R^{3+4.1}$
III-5	$R^{1.1.b}$ $R^{2.3}$ $R^{3.1}$ $R^{4.1}$
III-6	$R^{1.1.b}$ $R^{2.3}$ $R^{3+4.1}$
III-7	$R^{1.2.b}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
III-8	$R^{1.2.b}$ $R^{2.1}$ $R^{3+4.1}$
III-9	$R^{1.2.b}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
III-10	$R^{1.2.b}$ $R^{2.2}$ $R^{3+4.1}$
III-11	$R^{1.2.b}$ $R^{2.3}$ $R^{3.1}$ $R^{4.1}$
III-12	$R^{1.2.b}$ $R^{2.3}$ $R^{3+4.1}$
III-13	$R^{1.3.b}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
III-14	$R^{1.3.b}$ $R^{2.1}$ $R^{3+4.1}$
III-15	$R^{1.3.b}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
III-16	$R^{1.3.b}$ $R^{2.2}$ $R^{3+4.1}$
III-17	$R^{1.3.b}$ $R^{2.3}$
III-18	$R^{1.4.b}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
III-19	$R^{1.4.b}$ $R^{2.1}$ $R^{3+4.1}$

III-20	$R^{1.4.b}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
III-21	$R^{1.4.b}$ $R^{2.2}$ $R^{3+4.1}$
III-22	$R^{1.4.b}$ $R^{2.3}$
III-23	$R^{1.5.b}$ $R^{2.1}$ $R^{3.1}$ $R^{4.1}$
III-24	$R^{1.5.b}$ $R^{2.1}$ $R^{3+4.1}$
III-25	$R^{1.5.b}$ $R^{2.2}$ $R^{3.1}$ $R^{4.1}$
III-26	$R^{1.5.b}$ $R^{2.2}$ $R^{3+4.1}$
III-27	$R^{1.5.b}$ $R^{2.3}$

In any of these embodiments $R^{2.2}$ may be replaced by $R^{2.2.a}$.

For each embodiment according to any of the matrixes I, II or III (i.e. I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I-13, I-14, I-15, I-16, I-17, II-1, II-2, II-3, II-4, II-5, II-6, II-7, II-8, II-9, II-10, II-11, II-12, II-13, II-14, II-15, II-16, II-17, III-1, III-2, III-3, III-4, III-5, III-6, III-7, III-8, III-9, III-10, III-11, III-12, III-13, III-14, III-15, III-16, III-17, III-18, III-19, III-20, III-21, III-22, III-23, III-24, III-25, III-26, III-27) the definitions and preferences for each substituent as outlined above shall apply, exemplified with a non-limiting character as:

- For each substitution pattern for $\mathbf{R^1}$ the preferred number of halogen substituents at the 1 to 3 mandatory substituents **X** (= C_2-C_6-alkyl or C_1-C_6-alkoxy respectively, whatever is appropriate,) preferably are 2 to 6. More preferably the number is at least 2, more preferably 3 fluoro substituents. The preferred position for these halogen substituents are the alpha or more preferred the beta position of the C_2-C_6-alkyl residue or the beta position of the C_1-C_6-alkoxy residue (in particular it is referred to $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$, $\mathbf{R^{1.1.a}}$, $\mathbf{R^{1.2.a}}$, $\mathbf{R^{1.3.a}}$, $\mathbf{R^{1.1.b}}$, $\mathbf{R^{1.2.b}}$, $\mathbf{R^{1.3.b}}$, $\mathbf{R^{1.4.b}}$). Whenever **X** is C_1-C_6-alkoxy trifluoromethoxy is preferred. Whenever **X** is C_2-C_6-alkyl 2,2,2-trifluoreth-1-yl or 1,2,2,2-tetrafluoreth-1-yl or 1,1,2,2,2-pentafluoreth-1-yl is preferred, more preferred 2,2,2-trifluoreth-1-yl. For the embodiments with $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$, $\mathbf{R^{1.1.b}}$, $\mathbf{R^{1.2.b}}$, $\mathbf{R^{1.3.b}}$, $\mathbf{R^{1.4.b}}$ most preferred **X** is 1 substituent being trifluoromethoxy. For the embodiments with $\mathbf{R^{1.1.a}}$, $\mathbf{R^{1.2.a}}$, $\mathbf{R^{1.3.a}}$ most preferred **X** is 1 substituent being

2,2,2-trifluoreth-1-yl or 1,2,2,2-tetrafluoreth-1-yl or 1,1,2,2,2-pentafluoreth-1-yl 2,2,2-trifluoreth-1-yl.

- Most preferred **X** is 1 (one) trifluoromethoxy substituent such as outlined for $\mathbf{R^{1.5.b}}$.

- In each option for $\mathbf{R^1}$ (i.e. $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$, $\mathbf{R^{1.1.a}}$, $\mathbf{R^{1.2.a}}$, $\mathbf{R^{1.3.a}}$, $\mathbf{R^{1.1.b}}$, $\mathbf{R^{1.2.b}}$, $\mathbf{R^{1.3.b}}$, $\mathbf{R^{1.4.b}}$) at least one X preferably is in the ortho position to the C-atom of the phenyl-ring - the pyridylring respectively - by which $\mathbf{R^1}$ is attached to the methylene group which links $\mathbf{R^1}$ with the pyrazolopyrimidine group of the of formula I, e.g. $\mathbf{R^{1.5.b}}$.

- In each option for $\mathbf{R^1}$ (i.e. $\mathbf{R^{1.1}}$, $\mathbf{R^{1.2}}$, $\mathbf{R^{1.3}}$, $\mathbf{R^{1.1.a}}$, $\mathbf{R^{1.2.a}}$, $\mathbf{R^{1.3.a}}$, $\mathbf{R^{1.1.b}}$, $\mathbf{R^{1.2.b}}$, $\mathbf{R^{1.3.b}}$, $\mathbf{R^{1.4.b}}$) phenyl is preferred over pyridyl, with the substitution pattern as outlined above, e.g. $\mathbf{R^{1.5.b}}$.

- For each **of** $\mathbf{R^{2.1}}$, $\mathbf{R^{2.2}}$, $\mathbf{R^{2.3}}$ the preferred substitution pattern at phenyl and heteroaryl is 1 or 2 radical(s). Heteroaryl preferably is pyridyl.

For the purposes of the present invention, the substituents have the following meaning, unless specified otherwise:

C_1-C_6-Alkoxy is a straight-chain or branched alkoxy radical having 1 to 6, preferably 1 to 4, particularly preferably having 1 to 3 carbon atoms. Preferred examples include methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

C_1-C_6-Alkoxycarbonyl: C_{1-6}-Alkoxy is as defined for C_{1-6}-alkoxy.

C_1-C_6-Alkyl is a straight-chain or branched alkyl radical having 1 to 6, preferably 1 to 4, particularly preferably 1 to 3, carbon atoms. Preferred examples include methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

C_1-C_6-Alkylamino is a straight-chain or branched mono- or dialkylamino radical the alkyl group(s) therein having 1 to 6, preferably 1 to 4 and particularly preferably having 1 to 3 carbon atoms. Preferred examples include methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino and n-hexylamino, dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, di-t-butylamino, di-n-pentylamino, di-n-hexylamino, ethylmethylamino, isopropylmethylamino, n-butylethylamino and n-hexyl-i-pentylamino. In the context of the present invention it is understood that for each time this term is used, it shall be understood that this substituent may be mono-alkylamino (= C_{1-6}-Alkyl-NH-) and / or dialkylamino (= N-C_{1-6}-Alkyl-N (C_{1-6}-Alkyl)'-amino-). In the dialkyl-variation thereof, the two alkyl groups may be the same or different ones.

C_1-C_6-Alkylaminocarbonyl is a mono- or dialkylamino radical linked via a carbonyl group, where in the dialkyl variation thereof the alkyl radicals may be identical or different. The alkyl group(s) may be straight-chain or branched and each comprise 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms. In the context of the present invention it is understood that for each time this term is used, it shall be understood that this substituent may be mono-alkylaminocarbonyl (= C_{1-6}-Alkyl-NH-CO-) and / or dialkylamino.(= N-C_{1-6}-Alkyl-N-(C_{1-6}-Alkyl)'-N-CO-). In the dialkyl-variation thereof, the two alkyl groups may be the same or different ones. Preferred examples include methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, diisopropylaminocarbonyl, di-t-butylamino-carbonyl, di-n-pentylaminocarbonyl, di-n-hexylaminocarbonyl, ethylmethylaminocarbonyl, isopropylmethylaminocarbonyl, n-butylethylaminocarbonyl and n-hexyl-i-pentylaminocarbonyl. A further possibility in the case of a dialkylaminocarbonyl radical is for the two alkyl radicals to form together with the nitrogen atom to which they are bonded a 5- to 8-membered heterocyclyl. With regard to heterocyclyl it is referred to the definition said term. Preferred heterocyclyl in this context are morpholinyl and piperdinyl, more preferably morpholinyl.

C_1-C_6-Alkylcarbonylamino is an alkylcarbonyl radical linked via an amino group, where the alkyl radical may be straight-chain or branched and comprises 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3, carbon atoms. Preferred examples include methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, isopropylcarbonylamino, tert-butylcarbonylamino, n-pentylcarbonylamino and n-hexylcarbonylamino.

C_1-C_6-Alkylsulphonyl: The term C_1-C_6-alkyl stands for a straight-chain or branched alkyl-group linked via a sulphonyl (SO_2) radical to the phenyl or pyridyl. The C_1-C_6-alkyl having 1 to 6, preferably 1 to 4 and particularly preferably having 1 to 3, carbon atoms. Preferred examples include methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, tert-butylsulphonyl, n-pentylsulphonyl and n-hexylsulphonyl.

C_1-C_6-Alkylsulphonylamino is a C_1-C_6-Alkylsulphonyl linked via an Aminogroup to the phenyl or pyridyl. For C_1-C_6-Alkylsulphonyl see the corresponding definition. Preferred examples include methylsulphonylamino, ethylsulphonylamino, n-propylsulphonylamino, isopropyl-sulphonylamino, tert-butylsulphonylamino, n-pentylsulphonylamino and n-hexylsulphonylamino.

C_1-C_6-Alkylthio: The term C_1-C_6-alkyl stands for a straight-chain or branched alkyl-group linked via a sulphur (-S-) radical to the phenyl or pyridyl. The C_1-C_6-alkyl group having 1 to 6, preferably 1 to 4 and particularly preferably having 1 to 3, carbon atoms. Preferred examples include methylthio, ethylthio, n-propylthio, isopropylthio, tert-butylthio, n-pentylthio and n-hexylthio.

C_6-C_{10}-Arylaminocarbonyl is an arylamino radical linked via a carbonyl group. Preferred examples include phenylaminocarbonyl and naphthylaminocarbonyl.

C_6-C_{10}-Arylcarbonylamino is an arylcarbonyl radical linked via an amino group. Preferred examples include phenylcarbonylamino and naphthylcarbonylamino.

Halogen is fluorine, chlorine, bromine and iodine. Fluorine, chlorine, bromine are preferred, and fluorine and chlorine are particularly preferred.

Heteroaryl is an aromatic, mono- or bicyclic radical having 5 to 10 ring atoms and up to 5 heteroatoms from the series S, O and/or N. 5- to 6-membered heteroaryls having up to 4 heteroatoms are preferred. The heteroaryl radical may be bonded via a carbon or nitrogen atom. Preferred examples include thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl and isoquinolinyl.

6-membered heteroaryl is an aromatic radical having 6 ring atoms and up to 2 nitrogen atoms. The heteroaryl radical is bonded via a carbon atom. Preferred examples include pyridyl, pyrimidinyl, pyridazinyl and pyrazinyl.

Heteroarylaminocarbonyl is a heteroarylamino radical linked via a carbonyl group. For heteroaryl see the corresponding definition. Preferred examples include thienylaminocarbonyl, furylaminocarbonyl, pyrrolylaminocarbonyl, thiazolylaminocarbonyl, oxazolylaminocarbonyl, imidazolylaminocarbonyl, tetrazolylaminocarbonyl, pyridylaminocarbonyl, pyrimidinylaminocarbonyl, pyridazinylaminocarbonyl, indolylaminocarbonyl, indazolylaminocarbonyl, benzofuranylaminocarbonyl, benzothiophenylaminocarbonyl, quinolinylaminocarbonyl and isoquinolinylaminocarbonyl.

Heteroarylcarbonylamino is a heteroarylcarbonyl radical linked via an amino group. For heteroaryl see the corresponding definition. Preferred examples include thienylcarbonylamino, furylcarbonylamino, pyrrolylcarbonylamino, thiazolylcarbonylamino, oxazolylcarbonylamino, imidazolylcarbonylamino, tetrazolylcarbonylamino, pyridylcarbonylamino, pyrimidinylcarbonylamino, pyridazinylcarbonylamino, indolylcarbonylamino, indazolylcarbonylamino,

benzofuranylcarbonylamino, benzothiophenylcarbonylamino, quinolinylcarbonylamino and isoquinolinylcarbonylamino.

5- to 8-membered heterocyclyl is a mono- or polycyclic heterocyclic radical having 5 to 8 ring atoms and up to 3, preferably 2, heteroatoms or hetero groups from the series N, O, S, SO, SO_2. Mono- or bicyclic heterocyclyl is preferred. Monocyclic heterocyclyl is particularly preferred. N and O are preferred as heteroatoms. The heterocyclyl radicals may be saturated or partially unsaturated. Saturated heterocyclyl radicals are preferred. 5- to 7-membered heterocyclyl radicals are particularly preferred. Preferred examples include oxetan-3-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, tetrahydrofuranyl, tetrahydrothienyl, pyranyl, piperidinyl, thiopyranyl, morpholinyl, perhydroazepinyl. More preferred is morpholinyl.

When radicals in the compounds of the invention are optionally substituted, unless otherwise specified substitution by up to three identical or different substituents is preferred.

The term “compound” is understood in the chemical meaning as understood by the scientific chemical community.

It will be evident for the person skilled in the art, that some of the embodiments of the compounds of the invention may appear in tautomeric form(s) or stereoisomeric form(s) (enantiomers, diastereomers, racemates, mixtures thereof, etc.), which for example may exist in dependency of the substitution pattern. A stereochemically pure constituent can be isolated in a known manner from such mixtures of enantiomers and/or diastereomers.

Some embodiments of the compounds of the invention also may be transferred into physiologically acceptable salts.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

Such physiologically acceptable salts of the compounds of the present invention include salts with mineral acids, carboxylic acids and sulphonic acids, e.g. salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid, e.g. in the form of acid addition salts.

Physiologically acceptable salts of such embodiments of the present invention also may include salts with conventional bases such as, by way of example and preferably, alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonia, organic amines having 1 to 16 C atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methyl-morpholine, dehydroabietylamine, arginine, lysine, ethylenediamine and methylpiperidine.

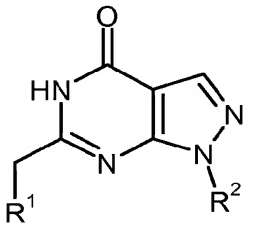
Some embodiments of compounds of the present invention may form solvates. For the purposes of the invention the term “solvates” refers to those forms of the compounds which form, in the solid or liquid state, a complex with solvent molecules. Hydrates are a specific form of solvates in which the coordination takes place with water. Typically a solvate is a crystalline complex of host molecules (compound molecules) and solvent molecules. The molecules of the solvent are incorporated into

the host lattice. The solvent molecules may - but need not - be linked to the host molecule by coordination. Solvates also may be formed by salt forms of the compounds of the present invention. Most interesting pharmaceutically acceptable solvates include hydrates or solvates with ethanol.

A derivative of a compound according to the invention which shares the same pharmacophoric group or groups and which thus provides a bioequivalent pharmacological effect may be considered a subgeneric form of said compound according to the invention.

The compounds of the present invention may be made in accordance with the outline of WO04099210 (in particular page 9, last paragraph to page 14, line 8, incorporated by reference). Specific procedures can be taken from the experimental part thereof.

A specific and independent embodiment EA according to the present invention refers to a compound, characterised by general formula I:



(I),

with

R^1

being phenyl or pyridyl, any of which is substituted with 1 to 4, preferably 1 to 3 substituents X ;

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6-alkylamino, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl,

C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by 1 to 3 radicals independently of one another selected from the group of hydroxy, cyano, halogen, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

X

independently of each other being selected from C_2-C_6-alkyl or C_1-C_6-alkoxy, where C_2-C_6-alkyl and C_1-C_6-alkoxy are at least dihalogenated up to perhalogenated and the halogen atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro, whereby at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferably at least twofold halogenated;

R^2

being phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6-alkylamino, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by one to three radicals independently of

one another selected from the group of hydroxy, cyano, halogen, hydroxy-carbonyl and a group of the formula $-NR^3R^4$,

R^3

being hydrogen or C_1-C_6-alkyl,

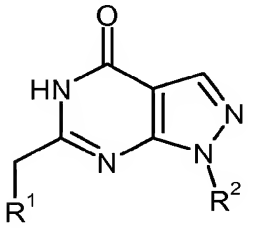
and R^4

being hydrogen or C_1-C_6-alkyl,

or R^3 and R^4 together with the nitrogen atom to which they are bonded are 5- to 8-membered heterocyclyl

and / or pharmaceutically acceptable salts thereof and / or solvates thereof

Yet a specific and independent embodiment EB according to the present invention refers to a compound characterised by general formula I:



(I),

with

R^1

being phenyl or pyridyl, any of which is substituted with 1 to 3 substituents X ;

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, cyano, trifluoromethyl, nitro, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl,

C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, and a group of the formula – NR^3R^4,

X

independently of each other being selected from C_2-C_6-alkyl or C_1-C_6-alkoxy, where C_2-C_6-alkyl and C_1-C_6-alkoxy are at least dihalogenated up to perhalogenated and the halogen atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro, whereby at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferably at least twofold halogenated;

R^2

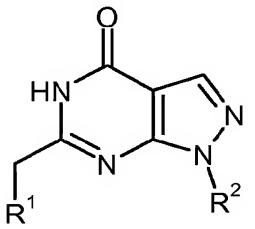
being phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6-alkylamino, halogen, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, and a group of the formula – NR^3R^4,

and the remaining characteristics as defined for embodiment EA

and / or pharmaceutically acceptable salts thereof and / or solvates thereof

Yet a specific and independent embodiment EC according to the present invention refers to a compound characterised by general formula I:



(I),

with

R^1

being phenyl or pyridyl, any of which is substituted with one to three substituents X;

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, trifluoromethyl, halogen,

X

independently of each other being selected from C_2-C_6-alkyl or C_1-C_6-alkoxy, where C_2-C_6-alkyl and C_1-C_6-alkoxy are at least dihalogenated up to perhalogenated and the halogen atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro, whereby at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is a least one fold or more preferably at least twofold halogenated;

R^2

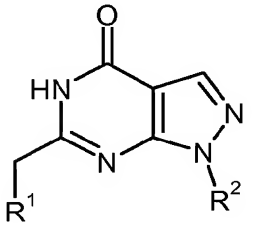
being phenyl or pyridyl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, trifluoromethyl, halogen and C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy and C_1-C_6-alkylthio, are optionally substituted by one to three halogen radicals,

and the remaining characteristics as defined for embodiment EA

and / or pharmaceutically acceptable salts thereof and / or solvates thereof

Yet a specific and independent embodiment ED according to the present invention refers to a compound characterised by general formula I:

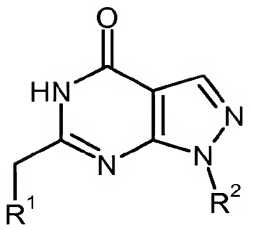


(I),

with

R^1 being phenyl or pyridyl any of which being substituted with 1 to 3 X whereas X being C_2-C_6-alkyl, preferably C_2-alkyl , with the further optional substitution pattern for C_2-C_6-alkyl and/or phenyl or C_2-C_6-alkyl and/or pyridyl and the remaining features as defined in any of the embodiments EA, EB or EC and / or pharmaceutically acceptable salts thereof and / or solvates thereof.

Yet a specific and independent embodiment EE according to the present invention refers to a compound characterised by general formula I:

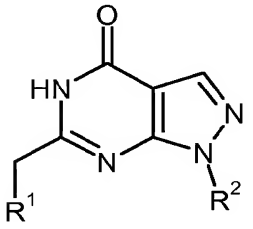


(I),

with

R^1 being phenyl or pyridyl, any of which being substituted with 1 to 3 X, whereas X being C_1-C_6-alkoxy, preferably C_1-alkoxy with the further optional substitution pattern for C_1-C_6-alkoxy and/or phenyl or C_1-C_6-alkoxy and/or pyridyl and the remaining features as defined for any of embodiments EA or EB and / or pharmaceutically acceptable salts thereof and / or solvates thereof.

Yet a specific and independent embodiment EF according to the present invention refers to a compound characterised by general formula I:



(I),

with

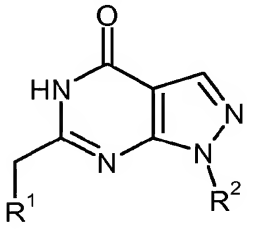
R^1

being phenyl or pyridyl, any of which must be substituted with 1 to 3 X, whereas X being C_1-C_6-alkoxy, substituted by at least 2, preferably 2 to 6 halogen atoms, selected from the group of fluoro, chloro and bromo, preferably fluoro substitutents, whereby preferably at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferred at least twofold halogenated;

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, trifluoromethyl, halogen,

and the remaining characteristics as defined in claim EA, EB, EC or EE and / or pharmaceutically acceptable salts thereof and / or solvates thereof.

Yet a specific and independent embodiment EG according to the present invention refers to a compound characterised by general formula I:

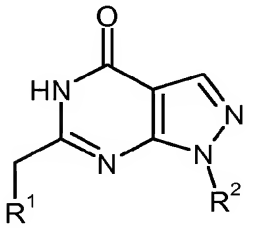


(I),

with

R^1 and R^2 as defined for any of the aforementioned embodiments EA, EB, EC, ED, EE or EF and for R^1 the substitution pattern at the one to 3 mandatory substituents X are at least 2, more preferably 3 fluoro substituents, whereby preferably at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferred at least twofold halogenated and / or pharmaceutically acceptable salts thereof and / or solvates thereof.

Yet a specific and independent embodiment EH according to the present invention refers to a compound characterised by general formula I:

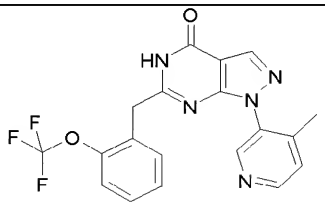
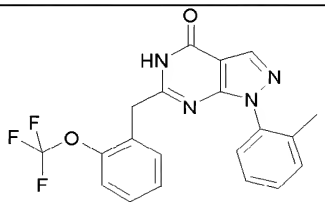
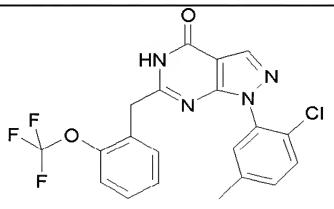
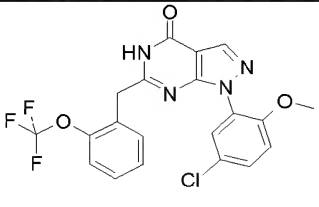


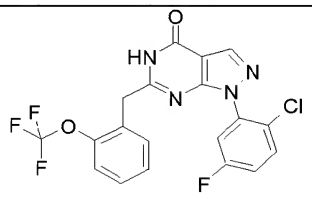
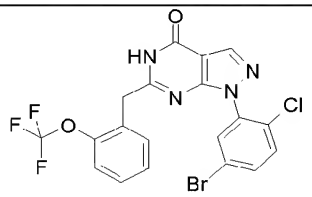
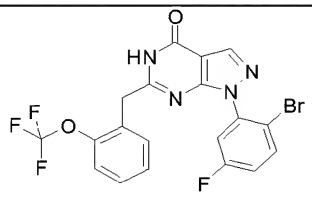
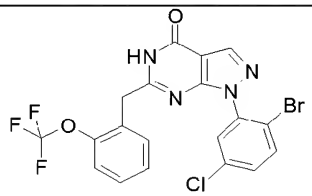
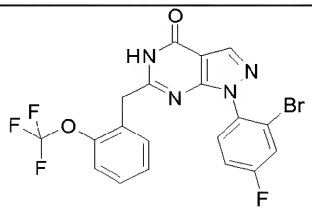
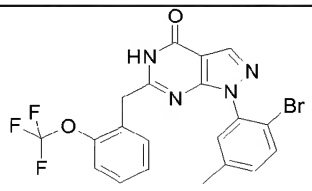
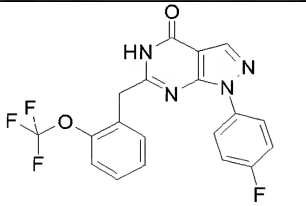
(I),

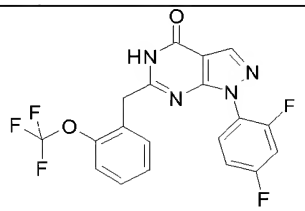
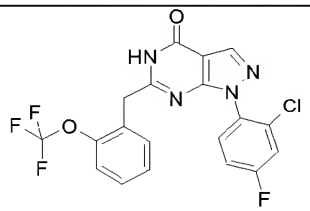
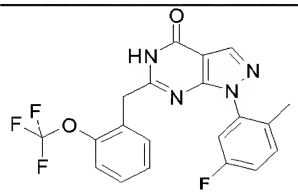
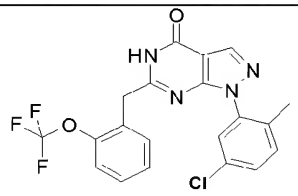
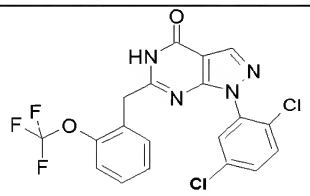
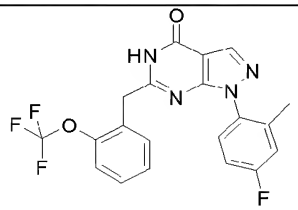
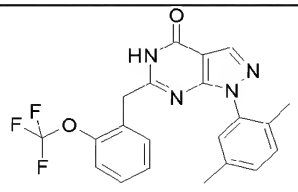
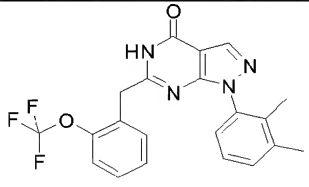
with

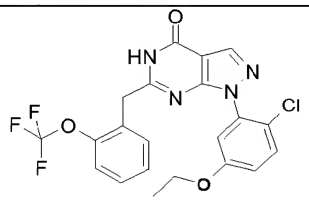
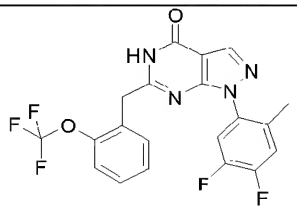
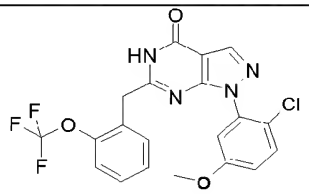
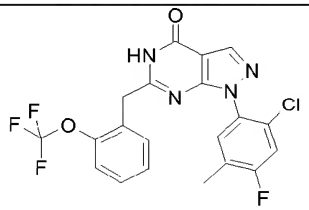
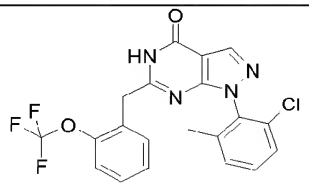
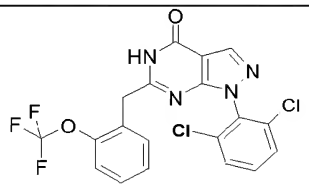
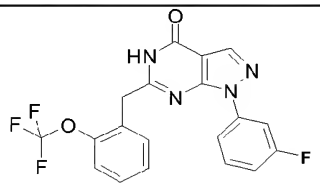
R^1 and R^2 as defined for any of the aforementioned embodiments EA, EB, EC, ED, EE, EF or EG with R^1 being phenyl substituted as defined in any of embodiments 1 to 5, preferably 2-trifluoromethoxyphenyl and / or pharmaceutically acceptable salts thereof and / or solvates thereof.

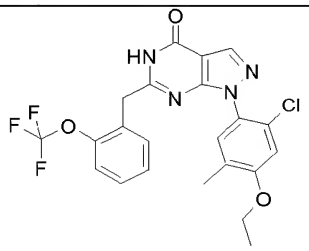
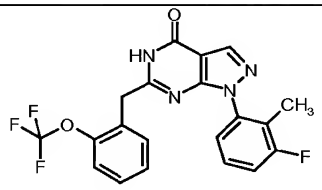
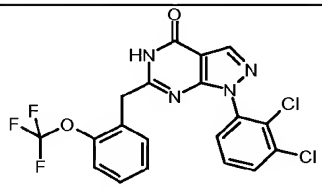
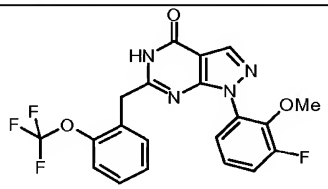
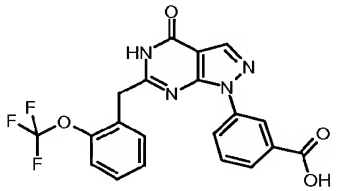
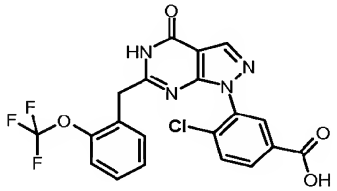
Preferred embodiments of the present invention are the following compounds, whereby each single compound is considered a specific and independent aspect of the present invention:

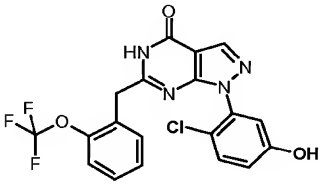
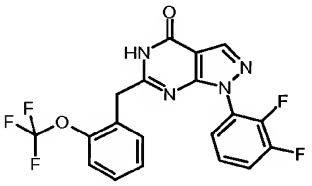
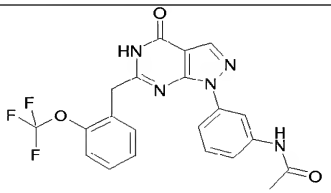
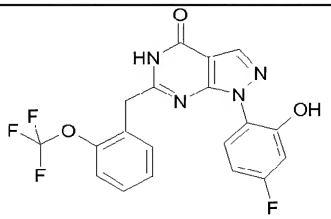
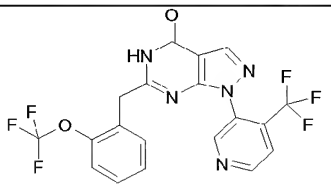
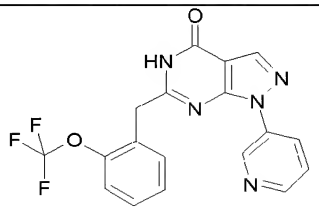
Compund	Structure	Name
1		1-(4-Methyl-pyridin-3-yl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
2		1-o-Tolyl-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d] pyrimidin-4-one
3		1-(2-Chloro-5-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
4		1-(5-Chloro-2-methoxy-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one

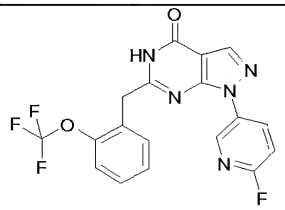
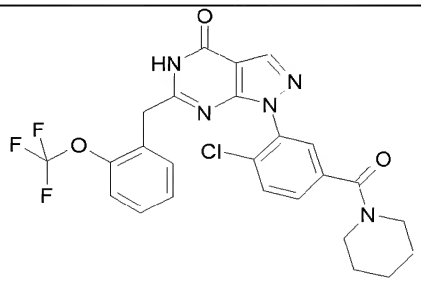
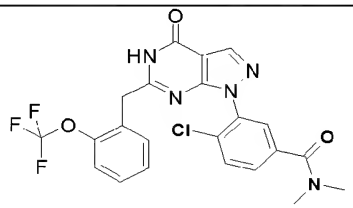
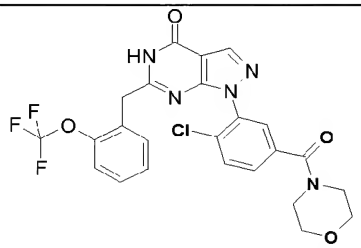
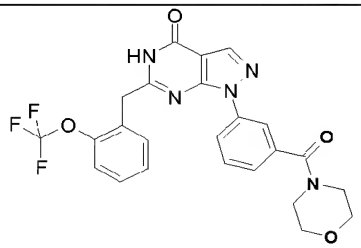
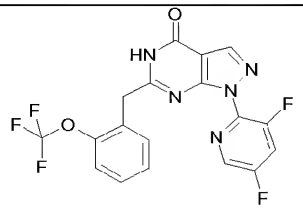
5		1-(2-Chloro-5-fluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
6		1-(5-Bromo-2-chloro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
7		1-(2-Bromo-5-fluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
8		1-(2-Bromo-5-chloro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
9		1-(2-Bromo-4-fluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
10		1-(2-Bromo-5-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
11		1-(4-Fluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one

12		1-(2,4-Difluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
13		1-(2-Chloro-4-fluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
14		1-(5-Fluoro-2-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
15		1-(5-Chloro-2-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
16		1-(2,5-Dichloro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
17		1-(4-Fluoro-2-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
18		1-(2,5-Dimethyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-ihydro-pyrazolo[3,4-d]pyrimidin-4-one
19		1-(2,3-Dimethyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one

20		1-(2-Chloro-5-ethoxy-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
21		1-(4,5-Difluoro-2-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
22		1-(2-Chloro-5-methoxy-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
23		1-(2-Chloro-4-fluoro-5-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
24		1-(2-Chloro-6-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
25		1-(2,6-Dichloro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
26		1-(3-Fluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one

27		1-(2-Chloro-4-ethoxy-5-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo [3,4-d]pyrimidin-4-one
28		1-(3-Fluoro-2-methyl-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
29		1-(2,3-Dichloro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
30		1-(2-Methoxy,3-fluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
30-1		1-(3-Carbox-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
30-2		1-(2-Chloro-5-carbox-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one

30-3		1-(2-Chloro-5-hydroxy-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
30-4		1-(2,3-Difluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
30-5		1-(3-Acetamido-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
31		1-(2-Hydroxy,4-fluoro-phenyl)-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
32		6-(2-Trifluoromethoxy-benzyl)-1-(4-trifluoromethyl-pyridin-3-yl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
33		6-(2-Trifluoromethoxy-benzyl)-1-(pyridin-3-yl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one

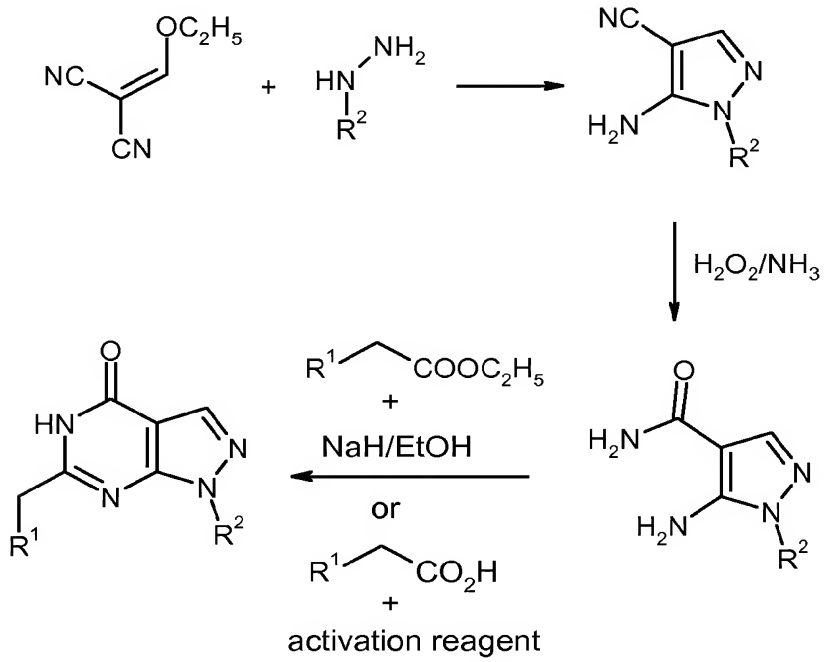
34		6-(2-Trifluoromethoxy-benzyl)-1-(4-fluoro-pyridin-3-yl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
35		1-[2-Chloro-5-(piperidine-1-carbonyl)-phenyl]-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
36		1-[2-Chloro-5-(dimethylamino-carbonyl)-phenyl]-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
37		1-[2-Chloro-5-(N-morpholino-carbonyl)-phenyl]-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
38		1-[3-(N-morpholino-carbonyl)-phenyl]-6-(2-trifluoromethoxy-benzyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one
39		6-(2-Trifluoromethoxy-benzyl)-1-(3,5-difluoro-pyridin-2-yl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one

and/or a pharmaceutically acceptable salt and/or a solvate thereof of each of the compounds where applicable.

Manufacture

The following scheme shall illustrate a process to manufacture the compounds of the present invention by way of example:

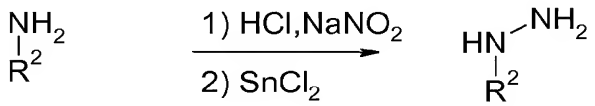
Scheme

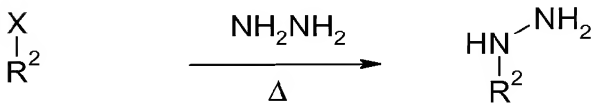


2-Ethoxymethylene-malononitrile is condensed with mono-substituted hydrazines to form 5-amino-1H-pyrazole-4-carbonitriles. The heterocycles are converted to the corresponding amides. Finally, reaction with carboxylic esters or carboxylic acids leads to pyrazolo[3,4-d]pyrimidin-4-ones as final products [cf., for example, A. Miyashita *et al.*, *Heterocycles* **1990**, *31*, 1309ff].

Mono-substituted hydrazine derivatives can be prepared either by formation of the diazonium salt and consequent reduction or, alternatively, by nucleophilic displacement on the corresponding halide derivative [cf., for example, I. Hunsberger *et al.*, *Journal of*

Organic Chemistry **1956**, *21*, 394-399; T. J. Fleck *et al.*, *Organic Process Research & Development* **2006**, *10*(2), 334-338].





X = F, Cl, Br, I

Further processes for preparing pyrazolo[3,4-d]pyrimidin-4-ones are known and can likewise be employed for synthesizing the compounds of the invention (see, for example: P. Schmidt *et al.*, *Helvetica Chimica Acta* **1962**, *189*, 1620ff.).

METHOD OF TREAMENT

The compounds of the invention show a valuable range of pharmacological effects which could not have been predicted. They are characterised in particular by inhibition of PDE9A.

In particular the compounds according to the present invention show a good selectivity profile in view of inhibiting or modulating specific members within the PDE9 family or other PDE families, with a preference (selectivity) towards PDE9A inhibition,.

To exemplify, but not meant to be limited, it now shall be referred to the selectivity of the PDE 9A inhibiting compounds according the present invention against PDE1C. Bingham *et al.* (*Biochem. Biophys. Res. Commun.*, **2006**, *350*, 25-32) described the expression pattern of PDE1C in human tissue. PDE1C shows highest expression in heart tissue followed by testis and vena cava.

Taken together the physiological role of PDE1C and the aspect of the present invention, namely to find compounds that can be used to treat conditions for which the inhibition of PDE9 is considered to be of advantage or that can be taken for the treatment of cognitive impairment, in particular Alzheimer's Disease, it will be appreciated that efficacy weighted against safety appears to be a feature to characterise the compounds of the invention.

It also will be acknowledged that the compounds of the present invention are supposed to show a good safety profile.

As mentioned before, the present invention refers to compounds, which are considered effective and selective inhibitors of phosphodiesterase 9A and can be used for the development of medicaments. Such medicaments shall preferably be used for the treatment of diseases in which the inhibition of PDE9A can evolve a therapeutic, prophylactic or disease modifying effect to the benefit of the patient.

Independently on the mode of action of the compounds, preferably medicaments with a compound according to the invention as active ingredient shall be used to treat, prevent or improve perception, concentration, cognition, learning or memory, like those occurring in particular in situations/diseases/syndromes such as mild cognitive impairment, age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

Another aspect of the present invention concerns the treatment of sleep disorders like insomnia or narcolepsy, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, including type 1 or type 2 diabetes, hyperglycemia, dyslipidemia, impaired

glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen or another disease which is accessible by PDE9A modulation.

A preferred condition, the course of which shall be influenced to the benefit of the patient by the use of the compounds according to the present invention is Alzheimer's Disease.

The use of the compounds of the present invention preferably is for the treatment, amelioration and / or prevention of the conditions as outlined herein, preferably for the treatment thereof, more preferably for the symptomatic treatment.

PHARMACEUTICAL COMPOSITIONS

Medicaments for administration comprise a compound of formula (I) in a therapeutically effective amount. By "therapeutically effective amount" it is meant that if the medicament is applied via the appropriate regimen adapted to the patient's condition, the amount of said compound of formula (I) will be sufficient to effectively treat, to prevent or to decelerate the progression of the corresponding disease, or otherwise to ameliorate the estate of a patient suffering from such a disease. It may be the case that the "therapeutically effective amount" in a mono-therapy will differ from the "therapeutically effective amount" in a combination therapy with another medicament.

The dose range of the compounds of general formula (I) applicable per day is usually from 0.1 to 5000 mg, preferably 0.1 to 1000 mg, preferably from 2 to 500 mg, more preferably from 5 to 250 mg, most preferably from 10 to 100 mg. A dosage unit (e.g. a tablet) preferably contains between 2 and 250 mg, particularly preferably between 10 and 100 mg of the compounds according to the invention.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age, weight, gender or other condition of the patient, route of administration, severity of disease, and the like.

The compounds according to the invention may be administered by oral, parenteral (intravenous, intramuscular etc.), intranasal, sublingual, inhalative, intrathecal, topical or rectal route. Suitable preparations for administering the compounds of formula (I) include for example patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions, suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.-%, preferably 0.1 to 50 wt.-% of the composition as a whole. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates or stabilisers such as alkali metal salts of ethylenediaminetetraacetic acid, optionally using emulsifiers and/or dispersants, while if water is used as diluent, for example, organic solvents may optionally be

used as solubilisers or dissolving aids, and the solutions may be transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

For oral use the tablets may obviously contain, in addition to the carriers specified, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additional substances such as starch, preferably potato starch, gelatin and the like. Lubricants such as magnesium stearate, sodium laurylsulphate and talc may also be used to produce the tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients.

The dosage of the compounds according to the invention is naturally highly dependent on the method of administration and the complaint which is being treated. When administered by inhalation the compounds of formula (I) are characterised by a high potency even at doses in the microgram range. The compounds of formula (I) may also be used effectively above the microgram range. The dosage may then be in the gram range, for example.

COMBINATIONS WITH OTHER ACTIVE SUBSTANCES

In another aspect the present invention relates to the above-mentioned pharmaceutical formulations as such which are characterised in that they contain a compound of formula I.

A further aspect of the present invention refers to a combination of at least one compound according to formula (I) with another compound selected from the group of for example beta-secretase inhibitors; gamma-secretase inhibitors; amyloid aggregation inhibitors such as e.g. alzhemed; directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants, such as e.g. vitamin E or ginkolide; anti-inflammatory substances, such as e.g. Cox inhibitors, NSAIDs additionally or exclusively having Aß lowering properties; HMG-CoA reductase inhibitors (statins); acetylcholinesterase inhibitors, such as donepezil, rivastigmine, tacrine, galantamine; NMDA receptor antagonists such as e.g. memantine; AMPA receptor agonists; AMPA receptor positive modulators, AMPkines, monoamine receptor reuptake inhibitors, substances modulating the concentration or release of neurotransmitters; substances inducing the secretion of growth hormone such as ibutamoren mesylate and capromorelin; CB-1 receptor antagonists or inverse agonists; antibiotics such as minocyclin or rifampicin; PDE2, PDE4, PDE5, PDE10 inhibitors, GABAA receptor inverse agonists, GABAA receptor antagonists, nicotinic receptor agonists or partial agonists or positive modulators, alpha4beta2 nicotinic receptor agonists or partial agonists or positive modulators, alpha7 nicotinic receptor agonists or partial agonists or positive modulators; histamine H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, alpha2-adrenoreceptor antagonists, calcium antagonists, muscarinic receptor M1 agonists or partial agonists or positive modulators, muscarinic receptor M2 antagonists, muscarinic receptor M4 antagonists, metabotropic glutamate-receptor 5 positive modulators, and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced.

This invention further relates to pharmaceutical compositions containing one or more, preferably one active substance, which is selected from the compounds according to

the invention and/or the corresponding salts, as well as one or more, preferably one active substance selected from among alzhemed, vitamin E, ginkolide, donepezil, rivastigmine, tacrine, galantamine, memantine, ibutamoren mesylate, capromorelin, minocyclin and/or rifampicin, optionally together with one or more inert carriers and/or diluents.

The compounds according to the invention may also be used in combination with immunotherapies such as e.g. active immunisation with Abeta or parts thereof or passive immunisation with humanised anti-Abeta antibodies or nanobodies for the treatment of the above-mentioned diseases and conditions.

The combinations according to the present invention may be provided simultaneously in one and the same dosage form, i.e. in form of a combination preparation, for example the two components may be incorporated in one tablet, e. g. in different layers of said tablet. The combination may be also provided separately, in form of a free combination, i.e the compounds of the present invention are provided in one dosage form and one or more of the above mentioned combination partners is provided in another dosage form. These two dosage forms may be equal dosage forms, for example a co-administration of two tablets, one containing a therapeutically effective amount of the compound of the present invention and one containing a therapeutically effective amount of the above mentioned combination partner. It is also possible to combine different administration forms, if desired. Any type of suitable administration forms may be provided.

The compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may be used simultaneously or at staggered times, but particularly close together in time. If administered simultaneously, the two active substances are given to the patient together; if administered at staggered times the two active substances are given to the patient successively within a period of less than or equal to 12, particularly less than or equal to 6 hours.

The dosage or administration forms are not limited, in the frame of the present invention any suitable dosage form may be used. Exemplarily the dosage forms may

be selected from solid preparations such as patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions, suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like.

The dosage forms are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of each active component being present. Depending from the administration route and dosage form the ingredients are selected accordingly.

The dosage for the above-mentioned combination partners is expediently 1/5 of the normally recommended lowest dose up to 1/1 of the normally recommended dose.

The dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily.

In accordance with this paragraph, one particular aspect of the invention is a medication consisting of - or the use of - a compound according to the invention, in particular in view of any of the aforementioned embodiments of matrix I, II or III, or any of the embodiments EA, EB, EC, ED, EF, EG, EH or the individually specified compounds, in combination with another therapeutically effective compound, preferably selected from the group of beta-secretase inhibitors; gamma-secretase inhibitors; amyloid aggregation inhibitors; directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants; anti-inflammatory substances; HMG-CoA reductase inhibitors, statins; acetylcholinesterase inhibitors, NMDA receptor antagonists; AMPA receptor agonists; AMPA receptor positive modulators, AMPkines, monoamine receptor reuptake inhibitors, substances modulating the concentration or release of neurotransmitters; substances modulating the secretion of growth hormone; CB-1 receptor antagonists or inverse agonists; antibiotics; PDE2, PDE4, PDE5, PDE10 inhibitors, GABAA receptor inverse agonists, GABAA receptor antagonists, nicotinic receptor agonists or partial agonists or positive modulators, alpha4beta2 nicotinic receptor agonists or partial agonists or positive modulators, alpha7 nicotinic receptor agonists or partial agonists or positive modulators;

histamine H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, alpha2-adrenoreceptor antagonists, calcium antagonists, muscarinic receptor M1 agonists or partial agonists or positive modulators, muscarinic receptor M2 antagonists, muscarinic receptor M4 antagonists, metabotropic glutamate-receptor 5 positive modulators, and / or other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced for the preparation of a medication for the treatment of a disease, in particular as herein described.

EXAMPLES

PHARMACEUTICAL COMPOSITIONS

The following examples of pharmaceutical formulations illustrate the present invention without restricting its scope:

Some examples of formulations will now be described, wherein the term "active substance" denotes one or more compounds according to the invention including the salts thereof. In the case of one of the aforementioned combinations with one or more other active substances the term "active substance" also includes the additional active substances.

Example A

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg

220.0 mg

Example B

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Example C

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance	150.0 mg
corn starch (dried)	approx. 80.0 mg
lactose (powdered)	approx. 87.0 mg
magnesium stearate	3.0 mg
	approx. 320.0 mg

Capsule shell: size 1 hard gelatine capsule.

Example D

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Example E

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

Example F

Ampoules containing 50 mg of active substance

Composition:

active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

The preparation of any the above mentioned formulations can be done following standard procedures.

BIOLOGICAL ASSAY

The in vitro effect of the compounds of the invention can be shown with the following biological assays.

PDE assay protocol:

The PDE enzymatic activity assays were run as SPA, in general according to the protocol of the manufacturer (Amersham Biosciences, product number: TRKQ 7100). As enzyme source, lysate (PBS with 1% Triton X-100 supplemented with protease inhibitors, cell debris removed by centrifugation at 13.000 rpm for 30 min) of SF 9 cell expressing the human PDE of interest was used. The total protein amount included in the assay varied upon infection and production efficacy of the SF9 cells and lay in the range of 0.1 – 100 ng.

In general, the assay conditions were as follows:

- total assay volume: 40 µl
- protein amount: 0.1 – 50 ng
- substrate concentration (cGMP or cAMP): 20 nM; ~1 mCi/l
- incubation time: 60 min at room temperature
- final DMSO concentration: 1%

The assays were run in 384-well format. The test reagents as well as the enyme and the substrate were diluted in assay buffer. The assay buffer contained 50 mM Tris, 8.3 mM MgCl2, 1.7 mM EGTA, 0.1 % BSA, 0.05 % Tween 20; the pH of assay buffer was adjusted to 7.5. In case activity of PDE1C was analysed, 50 nM Calmodulin and 3 mM CaCl2 were included in the assay buffer. In case PDE9 activity was analyzed, the reaction was stopped by applying a PDE9 specific inhibitor (e.g. compounds according to WO2004/099210). PDE1C was analysed with cAMP as substrate, and PDE9 was analyzed with cGMP as substrate.

Calculation of % inhibition:

The activity of the positive control (minus the negative control = background) is set to 100% and activity in the presence of test compound is expressed relative to these 100%.

Within this setting, an inhibition above 100% might be possible due to the nature of the variation of the positive control within the assay, however, in this case the reported % inhibition had been adjusted to 100%.

Calculation of IC50:

IC50 can be calculated in a conventional way, eventually with the help of GraphPadPrism or other suited software setting the positive control as 100 and the negative control as 0. For calculation of IC50 usually 8 dilutions of the test compound (substrates) are to be selected and tested following the aforementioned protocol.

5

For to illustrate the pharmacological properties of the compounds according to the present invention in the following are given some illustrative and representative examples thereof, which are not considered to be limiting.

Example No.	% inhibition PDE9A at 10 micromolar*	IC50 PDE9A (nanomolar)*	Selectivity* = IC 50 PDE 1C / IC 50 PDE9A (both nanomolar)
1	99	between 10 and 500	39
2	98	between 10 and 500	14
3	95	between 10 and 500	4
4	102	between 10 and 500	88
5	96	between 10 and 500	7
6	88	between 10 and 500	112
7	91	between 10 and 500	9
8	93	between 10 and 500	21
9	90	between 10 and 500	6
10	88	more than 500	7
11	47	more than 500	21
12	102	between 10 and 500	8
13	96	between 10 and 500	10
14	95	between 10 and 500	14
15	94	between 10 and 500	271
16	93	between 10 and 500	71
17	98	between 10 and 500	9
18	86	between 10 and 500	28
19	74	between 10 and 500	5
20	87	between 10 and 500	4
21	91	between 10 and 500	93
22	98	between 10 and 500	14
23	85	more than 500	46
24	87	more than 500	49
25	58	more than 500	24
26	51	more than 500	24
27	67	more than 500	14
28	96	between 10 and 500	8

29	89	between 10 and 500	9
30	95	between 10 and 500	8
30-1	101	between 10 and 500	55
30-2	100	between 10 and 500	55
30-3	100	between 10 and 500	14
30-4	99	between 10 and 500	3
30-5	97	between 10 and 500	26
31	82	more than 500	8
32	91	between 10 and 500	11
33	89	between 10 and 500	4
34	60	more than 500	19
35	93	between 10 and 500	10
36	98	between 10 and 500	54
37	99	between 10 and 500	27
38	92	more than 500	9
39	97	between 10 and 500	4

*for illustrative purposes

The in vivo effect of the compounds of this invention can be tested in the Novel Object Recognition test according to the procedure of Prickaerts *et al.* (*Neuroscience*, **2002**, *113*, 351-361).

CHEMICAL MANUFACTURE

Abbreviations:

DIPEA di-isopropyl-ethylamine
DMSO *dimethyl sulphoxide*
ESI *electrospray ionization (in MS)*
h *hour(s)*
HPLC *high performance liquid chromatography*
HPLC-MS *coupled high performance liquid chromatography-mass spectroscopy*
MPLC *medium pressure liquid chromatography*
min *minutes*
MS *mass spectroscopy*
Psi *pounds per square inch*

R_f	*retention factor*
RT	*retention time (in HPLC)*
TBTU	*2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate*
TFA	*trifluoroacetic acid*
TLC	*thin-layer chromatography*

LC-MS Methods:

Method 1

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Varian Microsorb 100 C18, 30 x 4.6 mm, 3.0 µm; eluent A: water + 0.13% TFA, eluent B: acetonitrile; gradient: 0.0 min 5% B → 0.18 min 5% B → 2.0 min 98% B → 2.2 min 98% B → 2.3 min 5% B → 2.5 min 5% B; flow rate: 3.5 ml/min; UV detection: 210-380 nm.

Method 2

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Merck Chromolith Performance RP18e, 100 x 1 mm; eluent A: water + 0.13% TFA, eluent B: acetonitrile; gradient: 0.0 min 5% B → 0.2 min 5% B → 1.6 min 98% B → 1.9 min 98% B → 2.0 min 5% B → 2.2 min 5% B; flow rate: 3.5 ml/min; UV detection: 210-380 nm.

Method 3

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, LCQduo Ion trap.; column: Sunryse MS-C18, 5 um, 4.6x100 mm; eluent A : 95%water + 5% acetonitrile + 20mM ammonium formate; eluent B: 95% acetonitrile +5%water + 20mM ammonium formate; gradient: A/B(95:5) for 1 min, then to A/B (5:95) in 7 min for 1.5 min; flow rate: 0.85 ml/min; UV detection: 254nm; Ion source: ESI.

Method Grad_C8_acidic

Instrument: LC/MS Waters. Hplc Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C8, 3.5um, 4.6x50 mm; eluent A: water + 0.1% TFA + 10% acetonitrile; eluent B:

acetonitrile; gradient: A/B (80:20), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 ml/min; UV Detection: 254nm; Ion source: ESI.

Method Grad_C8_NH4COOH

Instrument: LC/MS Waters. Hplc Alliance 2695 DAD, ZQ Quadrupole.Column: Xterra MS-C8, 3.5 um, 4.6x50 mm; eluent A : water + ammonium formate 5mM + 10% acetonitrile; eluent B : acetonitrile; gradient: A 100, then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 ml/min ; UV Detection: 254nm; Ion source: ESI.

Method Grad_C18_acidic

Instrument: LC/MS Waters. Hplc Alliance 2695 DAD, ZQ Quadrupole; column: Sunfire MS-C18, 3.5um, 4.6x50 mm; eluent A: water +0.1% TFA + 10% acetonitrile; eluent B: acetonitrile; gradient: A/B(80:20), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate:1.3 ml/min;; UV Detection: 254nm; Ion source: ESI.

Method 1D

Instrument:LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column: Sunfire MS-C18, 5 um, 4.6x100 mm; eluent A: 90% water +10% acetonitrile + ammonium formate 10mM; eluent B: acetonitrile 90%+10% water + ammonium formate 10mM; gradient: A(100) for 1 min, then to B (100) in 7 min for 1 min; flow rate: 1.2 mL/min; UV Detection: 254nm; Ion source: APCI.

Method 1E

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column: Symmetry C8, 5 um, 3x150 mm; eluent A: 90% water +10% acetonitrile + ammonium formate 10mM; eluent B= acetonitrile 90%+10% H_2O+NH_4COOH 10mM; gradient: A(100) for 1.5 min, then to B (100) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV Detection: 254nm; Ion source: APCI.

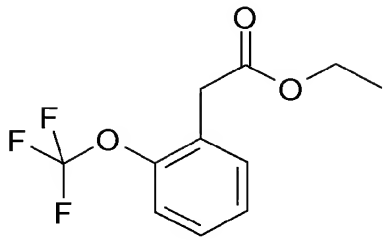
Microwave heating:

- Microwave apparatus type: Biotage Initiator Sixty.

- Discover® CEM instruments, equipped with 10 and 35 mL vessels;

Starting compounds:

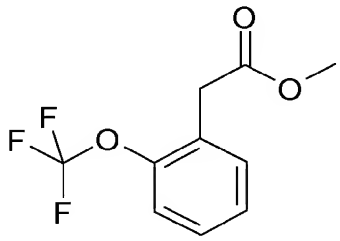
Example 1A



20.0 g (90.9 mmol) of (2-trifluoromethoxy-phenyl)-acetic acid were dissolved in 150 ml of absolute ethanol. At 0°C 10.0 ml (138 mmol) of thionylchloride were slowly added. The solution was heated to 50°C for 12 h. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. The remaining residue was dissolved in 10 ml of ethyl acetate and filtered through a pad of activated basic alumina. The ester was obtained as a colourless oil (18.4 g, 81% of theory).

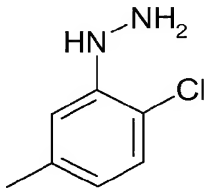
HPLC-MS (Method 1): RT: 1.64 min
MS (ESI pos): m/z = 249 $(M+H)^+$.

Example 1B



In analogy to the preparation of example 1A, the methyl ester was obtained using absolute methanol instead of ethanol.

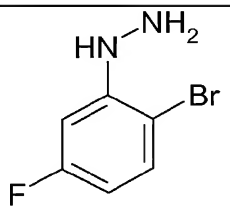
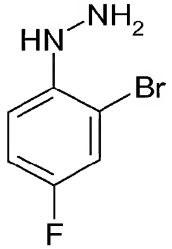
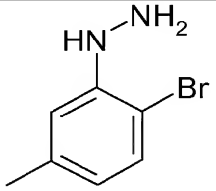
Example 2A

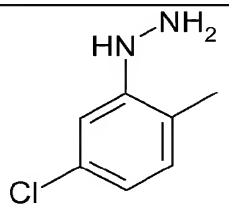
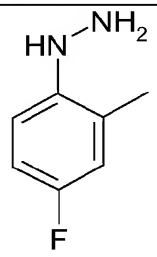
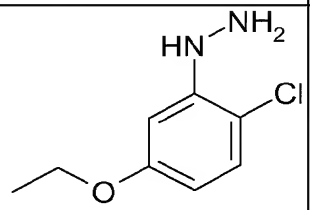
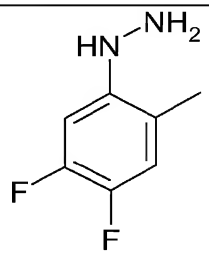
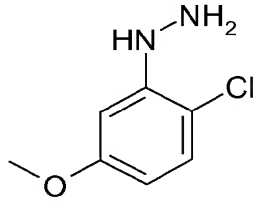
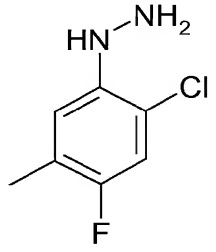


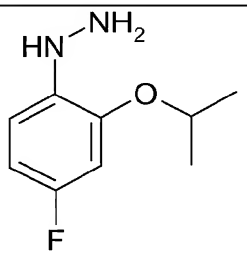
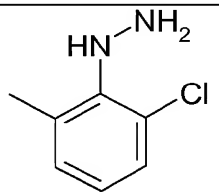
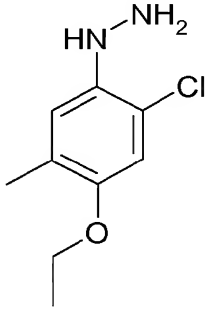
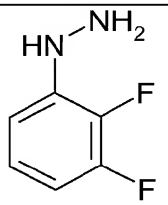
10.0 g (70.6 mmol) of 2-chloro-5-methyl-aniline were dissolved in 38 ml hydrochloric acid (20% in water). At -5°C a solution of 5.36 g (77.7 mmol) of sodium nitrite in 70 ml water was added drop wise within 40 min and kept at this temperature for further 30 min. The cold solution was added drop wise to a solution of 40.2 g (178 mmol) of tin(II)-chloride dihydrate in 48 ml of hydrochloric acid (32% in water), maintaining the temperature at -10°C. The resulting suspension was heated to 25°C and stirred for 12 h. The suspension was cooled to 0°C and 350 ml sodium hydroxide (40% in water) were added. The solution was extracted with ethyl acetate three times. The organic layers were collected, extracted with water and dried over magnesium sulphate. Filtration and evaporation of the solvent under reduced pressure yielded the hydrazine as a solid. (9.6 g, 87% of theory).

HPLC-MS (Method 1): RT: 0.90 min
MS (ESI pos): m/z = 157/159 (Cl) $(M+H)^+$ and 140/142 (Cl) $(M-NH_3+H)^+$.

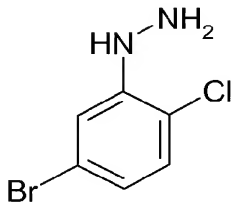
The following examples were synthesized in analogy to the preparation of example 2A, using the corresponding anilines as starting materials:

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 2B		2-Bromo-5-fluoro-phenylamine	0.83 (Method 1)	205/207 (Br) $(M+H)^+$ and 188/190 (Br) $(M-NH_3+H)^+$
Example 2C		2-Bromo-4-fluoro-phenylamine	0.81 (Method 1)	205/207 (Br) $(M+H)^+$ and 188/190 (Br) $(M-NH_3+H)^+$
Example 2D		2-Bromo-5-methyl-phenylamine (commercial from Anichem, North	0.96 (Method 1)	201/203 (Br) $(M+H)^+$ and 184/186 (Br) $(M-NH_3+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
		Brunswick, USA)		
Example 2D		5-Chloro-2-methyl-phenylamine	0.86 (Method 1)	
Example 2E		4-Fluoro-2-methyl-phenylamine	0.81 (Method 1)	141 $(M+H)^+$
Example 2F		2-Chloro-5-ethoxy-phenylamine	0.99 (Method 1)	187 $(M+H)^+$
Example 2G		4,5-Difluoro-2-methyl-phenylamine	0.88 (Method 1)	159 $(M+H)^+$
Example 2H		2-Chloro-5-methoxy-phenylamine	0.86 (Method 1)	173/175 (Cl) $(M+H)^+$
Example 2I		2-Chloro-4-fluoro-5-methyl-phenylamine	0.97 (Method 1)	

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 2J		4-Fluoro-2-isopropoxy-phenylamine	1.03 (Method 1)	
Example 2K		2-Chloro-6-methyl-phenylamine	0.76 (Method 1)	158/160 (Cl) $(M+H)^+$
Example 2L		2-Chloro-4-ethoxy-5-methyl-phenylamine	0.97 (Method 1)	
Example 2M		2,3-Difluoro-phenylamine		

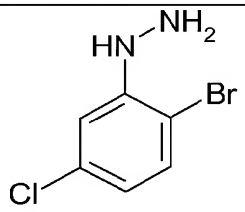
Example 3A



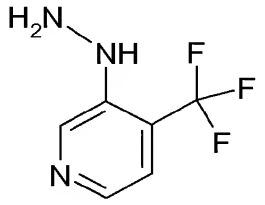
5.0 g (23.9 mmol) of 4-bromo-1-chloro-2-fluoro-benzene and 4.64 ml (95.5 mmol) of hydrazine hydrate were dissolved in 8 ml DMSO. The solution was stirred for 48 h at 70°C. The mixture was cooled to 25°C and water was added. The precipitate formed was collected by filtration and washed with water. After drying under reduced pressure the hydrazine was obtained as a solid. (2.6 g, 49% of theory).

HPLC-MS (Method 1): RT: 0.93 min
MS (ESI pos): m/z = 221/223/225 (Br,Cl) $(M+H)^+$ and 204/206/208 (Br,Cl) $(M-NH_3+H)^+$.

The following example was synthesized in analogy to the preparation of example 3A, using the corresponding aryl fluoride as starting material:

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 3B		1-bromo-4-chloro-2-fluoro-benzene	0.92 (Method 1)	221/223/225 (Br,Cl) $(M+H)^+$

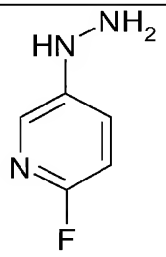
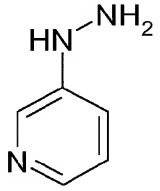
Example 4A



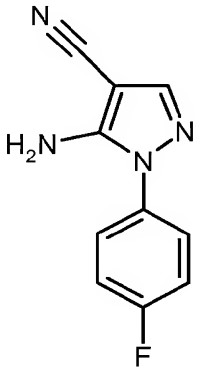
3.0 g (18.5 mmol) of 3-amino-4-(trifluoromethyl)-pyridine were dissolved in 15 ml hydrochloric acid (12N). The reaction mixture was cooled at -20°C; and then a solution of sodium nitrite (1.4 g; 20.35 mmol) in 15 ml of water was added dropwise, keeping the temperature at -15°C. After 1 hour, the reaction mixture was added drop wise to a solution of tin(II)-chloride dihydrate (12.53 g; 55.53 mmol) in 7.5 ml hydrochloric acid (12N) keeping the temperature at -15°C. After 1 hour the reaction was complete; the pH of the reaction mixture was adjusted to 10-11 by addition of 40% KOH at -20°C; the product was extracted by ethyl acetate. After drying under reduced pressure the hydrazine was obtained as a red solid. (2.5 g; 14.11 mmol; yield 76%).

HPLC-MS (Method 1E): RT: 4.48 min
MS (APCI): m/z = 178 (M+H)+.

The following examples were synthesized in analogy to the preparation of example 4A, using the corresponding aminopyridines as starting materials:

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 4B		6-Fluoro-pyridin-3-ylamine	0.45 (Method : Grad_C8_acidic)	128 (M+H)
Example 4C		Pyridin-3-ylamine	2.6 (Method 3)	110 $(M+H)^+$

Example 5A



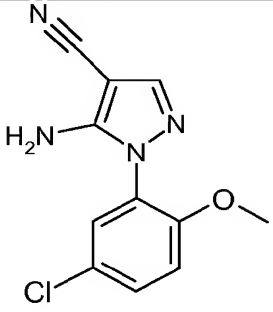
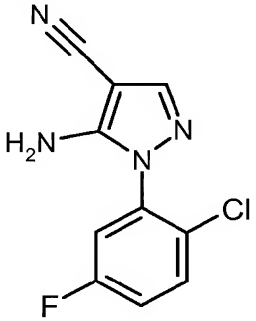
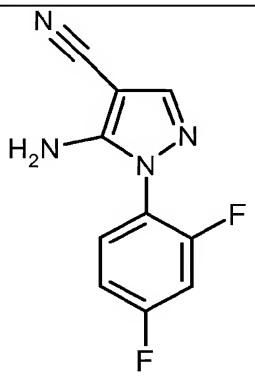
8.7 g (53.5 mmol) of 4-fluorphenylhydrazine hydrochloride was suspended with 6.5 g (53.5 mmol) of ethoxymethylenemalononitrile in 13 ml of ethanol, and 22.2 ml (160 mmol) of triethylamine were added. The reaction mixture was heated to 50°C for 2 h. After cooling to room temperature the solvent was removed under reduced pressure. The remaining residue was treated with water (25 ml) and extracted three times with ethyl acetate. The organic layer was dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure. The remaining residue was

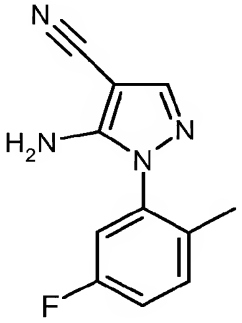
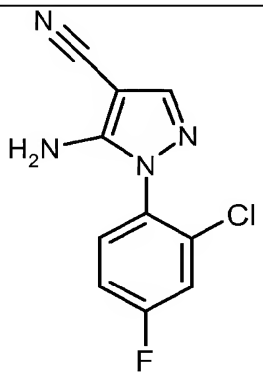
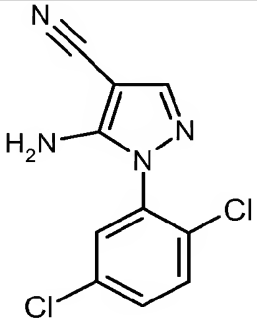
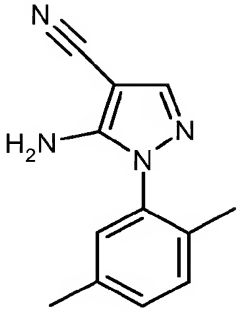
purified by preparative MPLC (SiO_2, eluent CH_2Cl_2). 5.0 g (46% of theory) of the product were obtained as an oil, that solidifies over night.

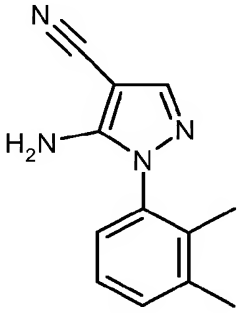
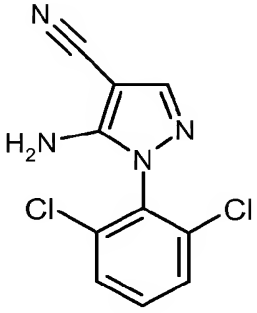
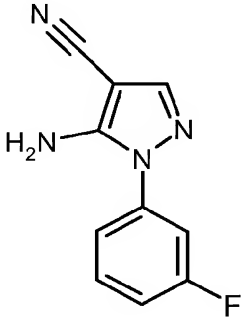
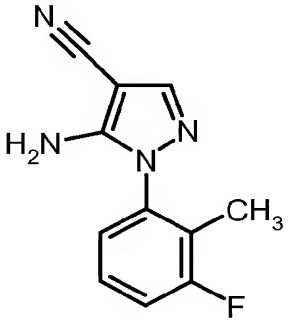
LC-MS (Method 1): RT = 1.06 min

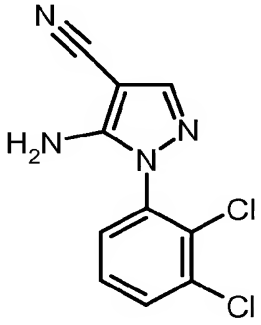
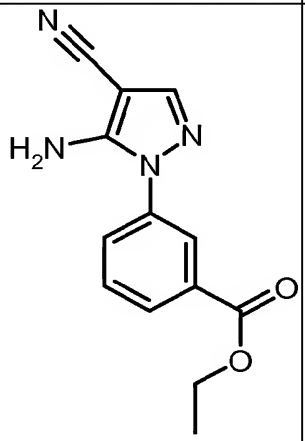
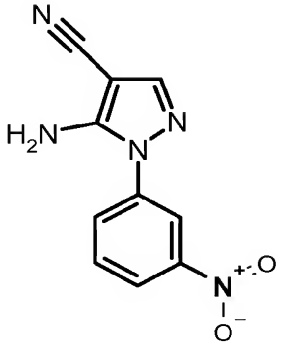
MS (ESI pos): m/z = 203 $(M+H)^+$.

The following examples were synthesized in analogy to the preparation of example 5A, using the corresponding hydrazines as starting materials:

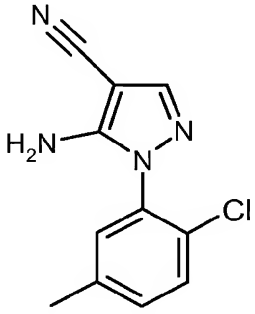
	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 5B		(5-Chloro-2-methoxy-phenyl)-hydrazine hydrochloride (commercial from ACB Blocks Ltd., Moscow, Russia)	1.27 (Method 1)	249/251 (Cl) $(M+H)^+$
Example 5C		(2-Chloro-5-fluoro-phenyl)-hydrazine hydrochloride (commercial from Apollo Scientific, Cheshire, UK)	1.13 (Method 1)	237/239 (Cl) $(M+H)^+$
Example 5D		(2,4-Difluoro-phenyl)-hydrazine hydrochloride	1.05 (Method 1)	221 $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 5E		(5-Fluoro-2-methyl-phenyl)-hydrazine hydrochloride	1.18 (Method 1)	217 $(M+H)^+$
Example 5F		(2-Chloro-5-fluoro-phenyl)-hydrazine hydrochloride	1.15 (Method 1)	237/239 (Cl) $(M+H)^+$
Example 5G		(2,5-Dichloro-phenyl)-hydrazine hydrochloride	1.28 (Method 1)	254/256/258 (2Cl) $(M+H)^+$
Example 5H		(2,5-Dimethyl-phenyl)-hydrazine hydrochloride	1.02 (Method 1)	231 $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 5I		(2,3-Dimethyl-phenyl)-hydrazine hydrochloride	1.23 (Method 1)	213 $(M+H)^+$
Example 5J		(2,6-Dichloro-phenyl)-hydrazine hydrochloride	1.23 (Method 1)	254/256/258 (2 Cl) $(M+H)^+$
Example 5K		(3-Fluoro-phenyl)-hydrazine hydrochloride	1.16 (Method 1)	203 $(M+H)^+$
Example 5L		(3-Fluoro-2-methyl-phenyl)-hydrazine hydrochloride (commercial from Matrix Scientific, Columbia, USA), US2002/169163	1.08 (Method 1)	215 $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 5M		(2,3-Dichloro-phenyl)-hydrazine hydrochloride	1.24 (Method 1)	251/253 (2Cl) $(M+H)^+$
Example 5N		3-Hydrazino-benzoic acid ethyl ester hydrochloride	1.25 (Method 1)	257 $(M+H)^+$
Example 5O		3-Nitrophenylhydrazine hydrochloride	1.16 (Method 1)	

Example 6A

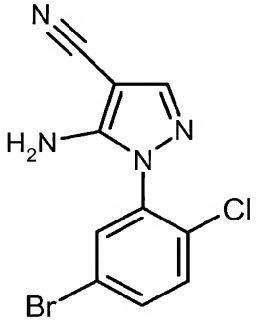


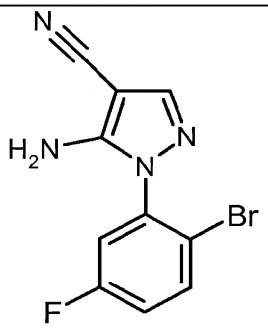
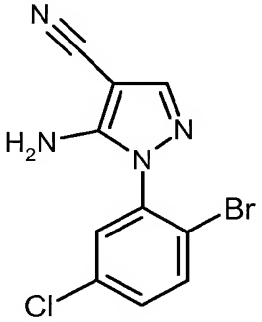
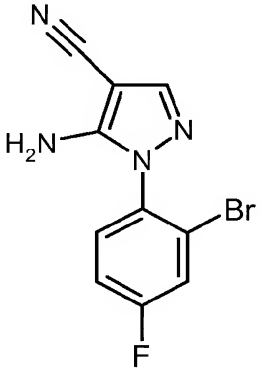
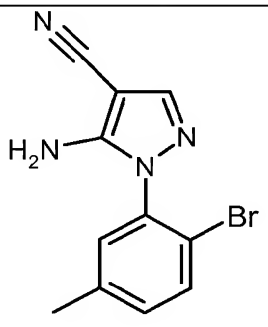
9.6 g (61.3 mmol) of example 2A and 7.49 g (61.3 mmol) of ethoxymethylenemalononitrile in 15 ml of ethanol, and 17.0 ml (123 mmol) of triethylamine were added. The reaction mixture was heated to 50°C for 3h. After cooling to room temperature the solvent was removed under reduced pressure. The remaining residue was dissolved in ethyl acetate and extracted twice with a saturated aqueous solution of sodium hydrogen carbonate. The organic layer was dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure. The remaining residue was purified by preparative MPLC (SiO_2, eluent CH_2Cl_2). 7.2 g (51% of theory) of the product were obtained as an oil, that solidifies over night.

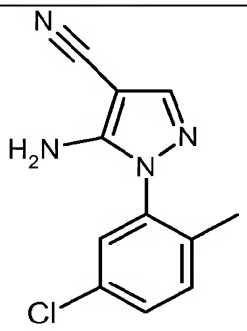
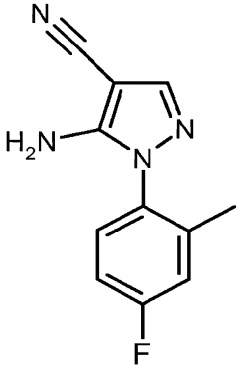
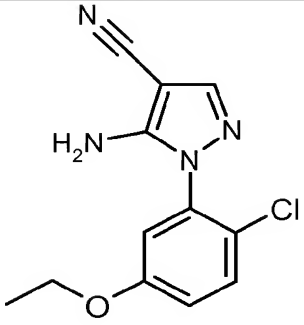
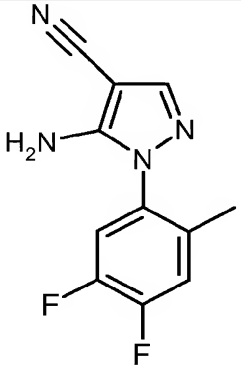
LC-MS (Method 1): RT = 1.26 min

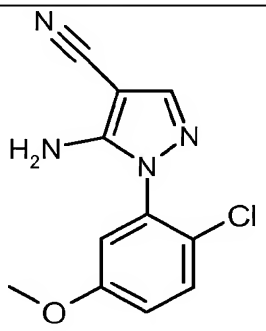
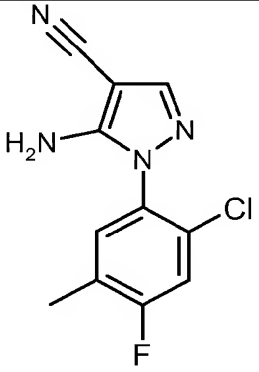
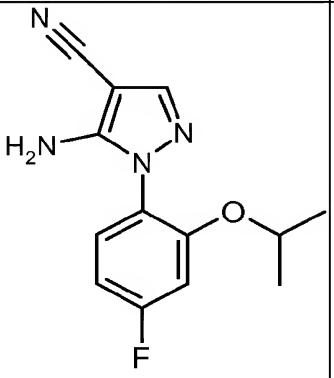
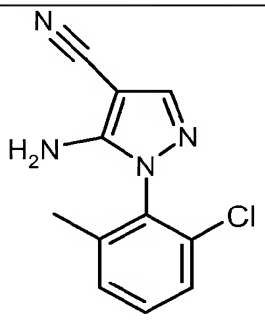
MS (ESI pos): m/z = 233/235 (Cl) $(M+H)^+$.

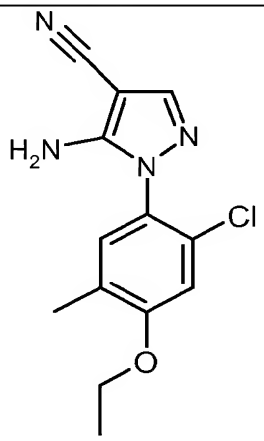
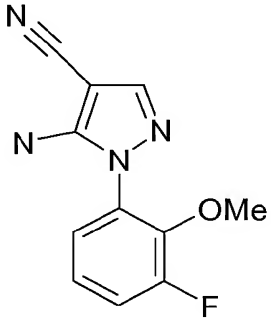
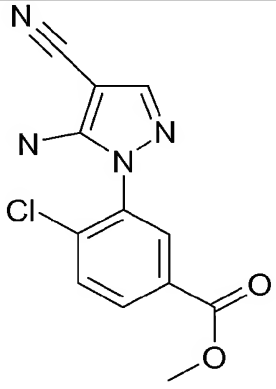
The following examples were synthesized in analogy to the preparation of example 6A, using the corresponding hydrazines as starting materials:

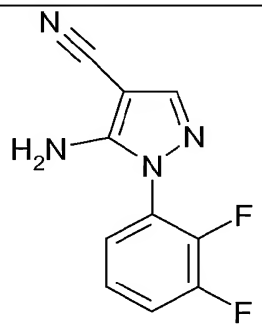
	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 6B		Example 3A	1.32 (Method 1)	297/299/301 (Br,Cl) $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 6C		Example 2B	1.31 (Method 1)	281/283 (Br) $(M+H)^+$
Example 6D		Example 3B	1.34 (Method 1)	297/299/301 (Br,Cl) $(M+H)^+$
Example 6E		Example 2C	1.18 (Method 1)	281/283 (Br) $(M+H)^+$
Example 6F		Example 2D	1.25 (Method 1)	277/279 (Br) $(M+H)^+$

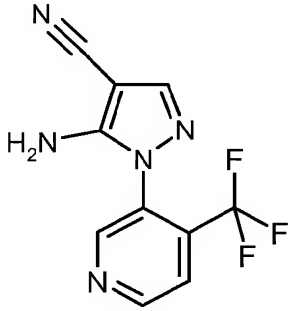
	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 6G		Example 2D	1.32 (Method 1)	234/236 (Cl) $(M+H)^+$
Example 6H		Example 2E	1.17 (Method 1)	217 $(M+H)^+$
Example 6I		Example 2F	1.33 (Method 1)	263/265 (Cl) $(M+H)^+$
Example 6J		Example 2G	1.23 (Method 1)	235 $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 6K		Example 2H	1.19 (Method 1)	249/251 (Cl) $(M+H)^+$
Example 6L		Example 2I	1.31 (Method 1)	251/253 (Cl) $(M+H)^+$
Example 6M		Example 2J	1.36 (Method 1)	261 $(M+H)^+$
Example 6N		Example 2K	1.23 (Method 1)	233/235 (Cl) $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 6O		Example 2L	1.31 (Method 1)	251/253 (Cl) $(M+H)^+$
Example 6P		(3-Fluoro-2-methoxy-phenyl)-hydrazine (commercial from_____Beta Pharma, Inc., New Haven, CT, USA)	1.06 (Method 1)	233 $(M+H)^+$
Example 6Q		4-chloro-3-hydrazino-benzoic acid ethyl ester hydrochloride	1.22 (Method 1)	277/279 (Cl) $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 6R		Example 2M		

Example 7A



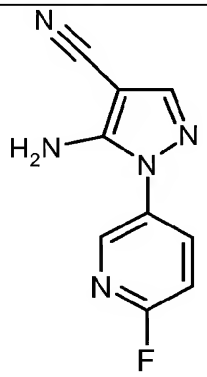
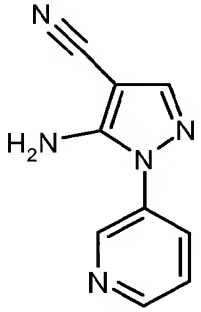
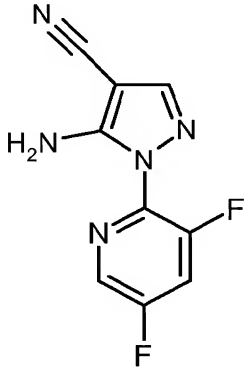
To a solution of example 4A (2.5 g; 14.11 mmol) in ethyl alcohol (170 ml) ethoxymethylenemalononitrile (1.72 g; 14.11 mmol) was added in portions and then the reaction mixture was refluxed during one hour. The reaction mixture was then allowed to reach room temperature observing the formation of a solid that was filtered off and purified by flash chromatography. 2.2g of the desired compound were obtained (8.68 mmol; yield = 61.6%).

LC-MS (Method Grad-C8-NH4COOH): RT = 1.88 min

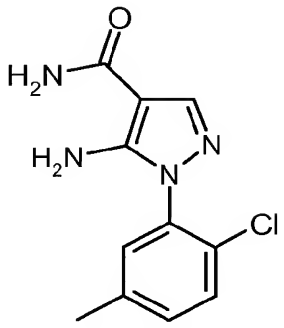
MS (ESI pos): m/z = 254 $(M+H)^+$.

The following examples were synthesized in analogy to the preparation of example 7A, using the corresponding hydrazines as starting materials:

5

	structure	starting material	RT [min]	MS (m/z)
Example 7B		Example 4B	1.12 (Method Grad_C18_acidic)	204 $(M+H)^+$ ESI
Example 7C		Example 4C	3.50 (Method 1E)	186 $(M+H)^+$ APCI
Example 7D		3,5-Difluoro-2hydrazinopyridine (Apollo Scientific Fluorine Chemicals)	2.22 (Method Grad_C8__NH4COOH)	221 $(M+H)^+$ ESI

Example 8A

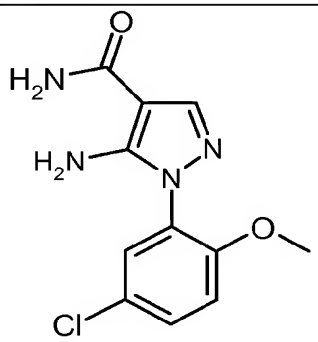


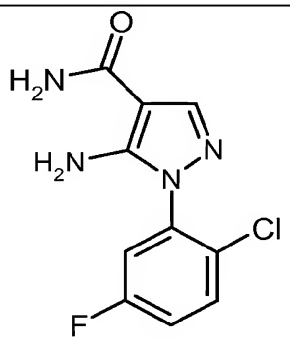
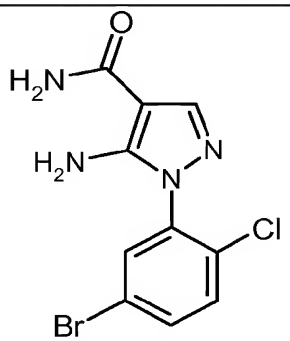
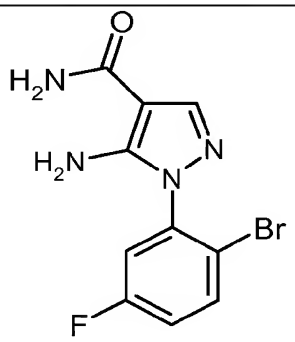
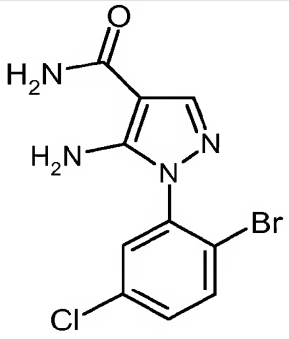
7.2 g (31.0 mmol) of example 6A was dissolved in 250 ml of ethanol. At 25°C a solution of 66.5 ml (0.77 mol) hydrogenperoxide (35% in water) in 300 ml ammonia (25% in water) was added slowly over a period of 10 min. The solution was carefully concentrated to a volume of 30 ml under reduced pressure. The precipitate formed was collected by filtration and purified by preparative HPLC (eluent A: water + 0.13% TFA, eluent B: acetonitrile). 5.8 g (75% of theory) of the product were obtained as a colourless solid.

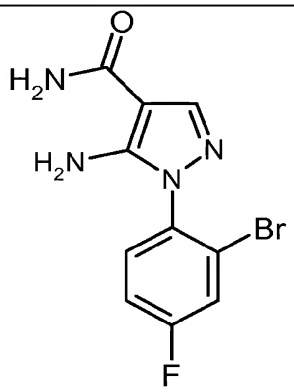
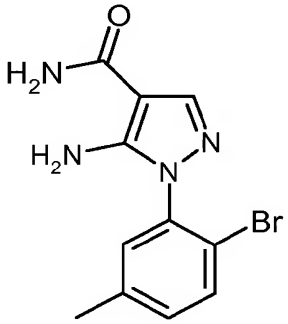
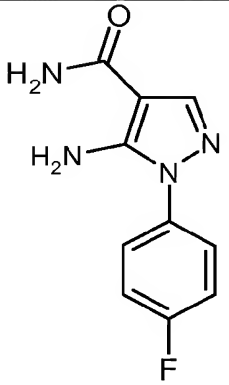
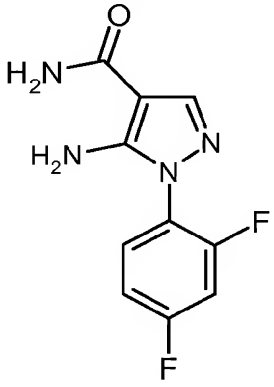
LC-MS (Method 1): RT = 0.66 min

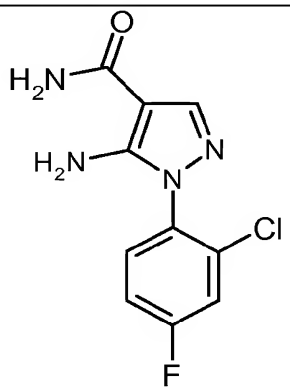
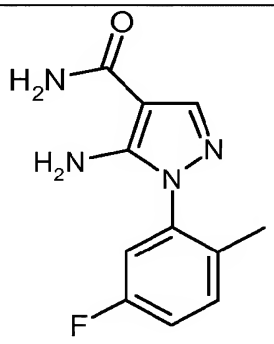
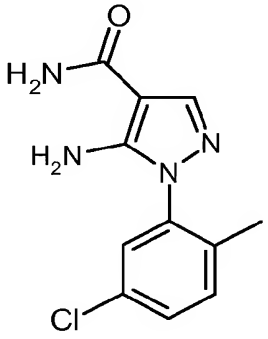
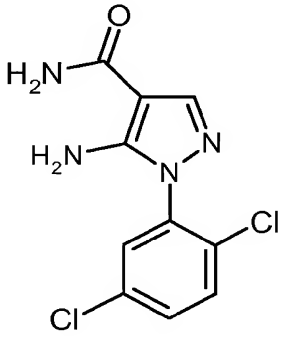
MS (ESI pos): m/z = 251/253 (Cl) $(M+H)^+$.

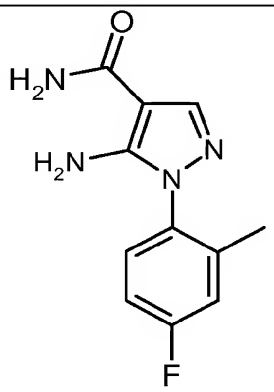
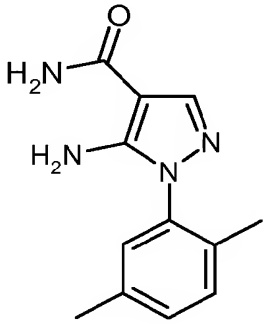
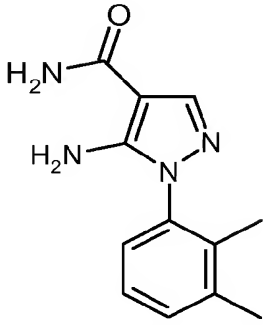
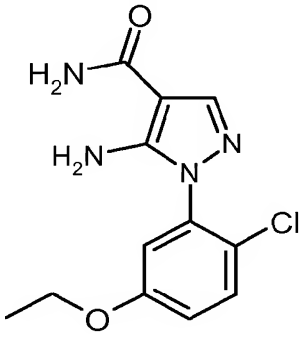
The following examples were synthesized in analogy to the preparation of example 8A, using the corresponding 5-amino-1H-pyrazole-4-carbonitriles as starting materials:

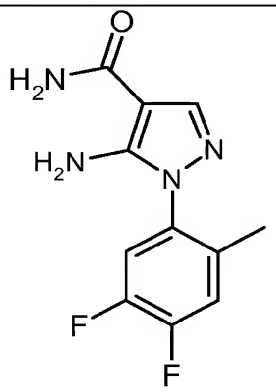
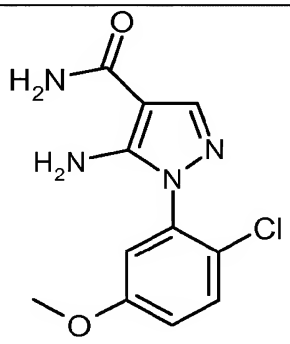
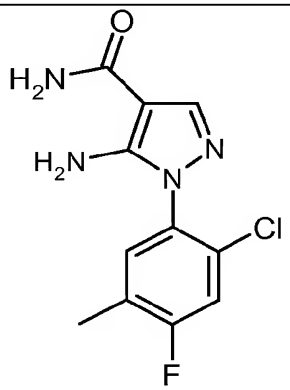
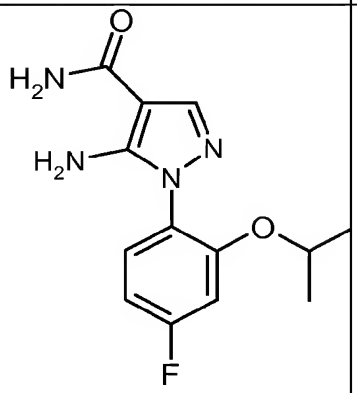
	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 8B		Example 5B	1.05 (Method 1)	267/269 (Cl) $(M+H)^+$

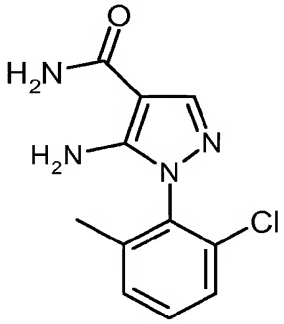
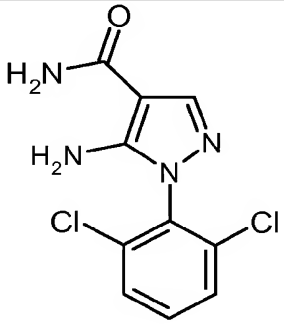
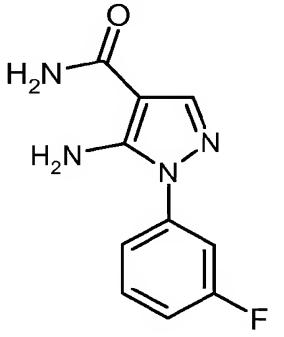
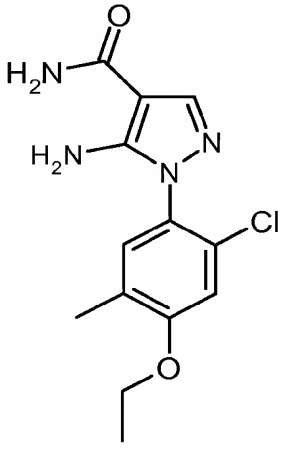
	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 8C		Example 5C	0.94 (Method 1)	255/257 (Cl) $(M+H)^+$
Example 8D		Example 6B	1.09 (Method 1)	315/317/319 (Br,Cl) $(M+H)^+$
Example 8E		Example 6C	0.88 (Method 1)	299/301 (Br) $(M+H)^+$
Example 8F		Example 6D	1.08 (Method 1)	315/317/319 (Br,Cl) $(M+H)^+$

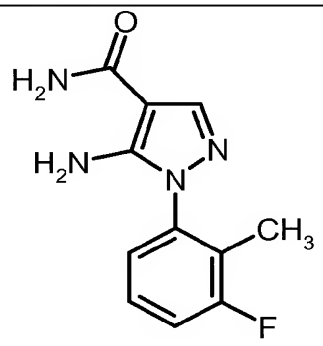
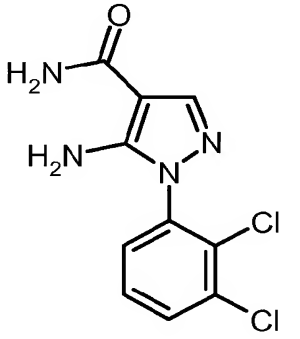
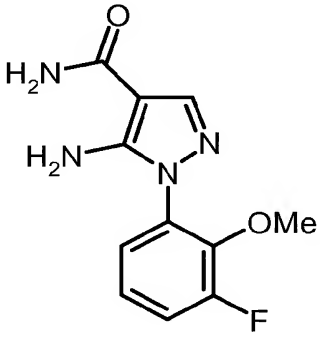
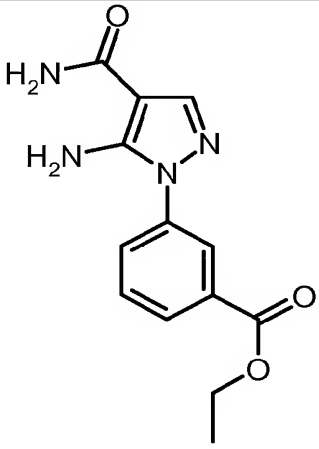
	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 8G		Example 6E	0.94 (Method 1)	299/301 (Br) $(M+H)^+$
Example 8H		Example 6F	1.06 (Method 1)	295/297 (Br) $(M+H)^+$
Example 8I		Example 5A	0.89 (Method 1)	221 $(M+H)^+$
Example 8J		Example 5D	0.86 (Method 1)	239 $(M+H)^+$

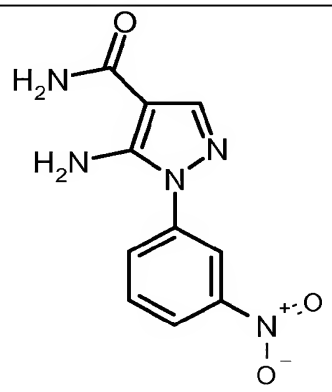
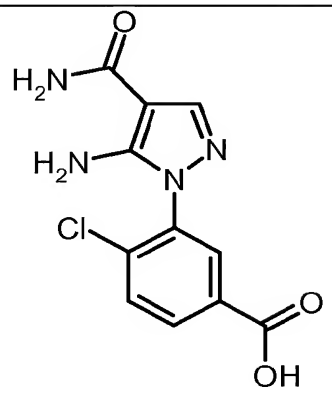
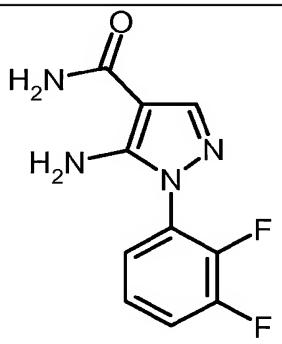
	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 8K		Example 5F	0.94 (Method 1)	255/257 (Cl) $(M+H)^+$
Example 8L		Example 5E	0.93 (Method 1)	235 $(M+H)^+$
Example 8M		Example 6G	1.08 (Method 1)	251/253 (Cl) $(M+H)^+$
Example 8N		Example 5G	1.06 (Method 1)	272/274/276 (2Cl) $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 8O		Example 6H	0.96 (Method 1)	235 $(M+H)^+$
Example 8P		Example 5H	1.02 (Method 1)	231 $(M+H)^+$
Example 8Q		Example 5I	0.99 (Method 1)	231 $(M+H)^+$
Example 8R		Example 6I	1.10 (Method 1)	281/283 (Cl) $(M+H)^+$

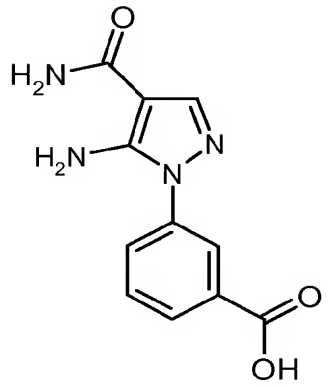
	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 8S		Example 6J	1.00 (Method 1)	253 $(M+H)^+$
Example 8T		Example 6K	0.99 (Method 1)	267/269 (Cl) $(M+H)^+$
Example 8U		Example 6L	1.08 (Method 1)	269/271 (Cl) $(M+H)^+$
Example 8V		Example 6M	1.13 (Method 1)	279 $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 8W		Example 6N	0.96 (Method 1)	251/253 (Cl) $(M+H)^+$
Example 8X		Example 5J	0.94 (Method 1)	271/273/275 (2Cl) $(M+H)^+$
Example 8Y		Example 5K	0.95 (Method 1)	221 $(M+H)^+$
Example 8Z		Example 6O	1.08 (Method 1)	269/271 (Cl) $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 8AA		Example 5L	0.92 (Method 1)	235 $(M+H)^+$
Example 8AB		Example 5M	1.02 (Method 1)	271/273 (2Cl) $(M+H)^+$
Example 8AC		Example 6P	0.86 (Method 1)	251 $(M+H)^+$
Example 8AD		Example 5N	1.08 (Method 1)	275 $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 8AE		Example 5O	0.95 (Method 1)	
Example 8AF		Example 6Q	0.86 (Method 1)	281/283 (Cl) $(M)^+$
Example 8AJ		Example 6R		

Example 8AG

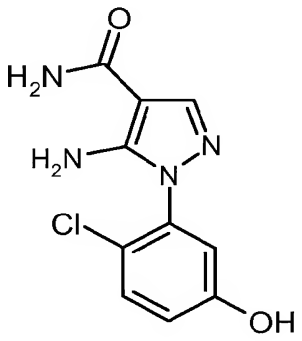


0.90 g of example 8 AD (3.50 mmol) were dissolved in 20 mL ethanol and 12 mL 2N NaOH solution was added. The mixture was stirred at room temperature for 2 h. The precipitate forming was filtered off and dried to give 0.60 g (70%) of example 8AG.

LC-MS (Method 1): RT = 0.80 min

MS (ESI pos): m/z = 245 (M-H)-.

Example 8AH

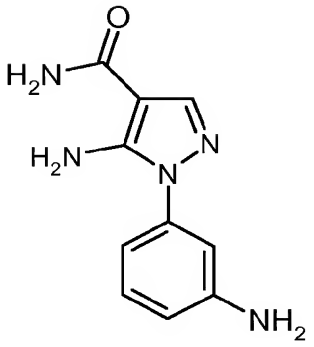


0.25 g of example 8R (0.89 mmol) were dissolved in 2 mL dichloromethane and 2.5 mL BBr3 solution (1M in THF) was added. The mixture was stirred at room temperature for 48 h. Standard aqueous work up afforded 0.10 g (44%) of example 8 AH.

LC-MS (Method 1): RT = 0.82 min

MS (ESI pos): m/z = 252/254 (Cl) (M)+.

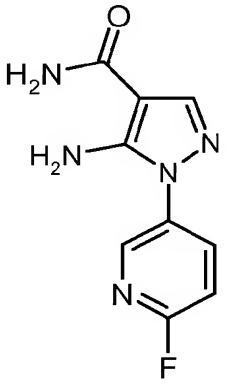
Example 8AI



4.79 g of example 8AE (19.0 mmol) were dissolved in 500 mL methanol and 1.0 g PD/C (10%) was added. The mixture was hydrogenated at room temperature for 4 h at 60 psi hydrogen pressure. Filtration and concentration afforded 4.06 g (98%) of example 8 AI.

LC-MS (Method 1): RT = 0.36 min

Example 9A

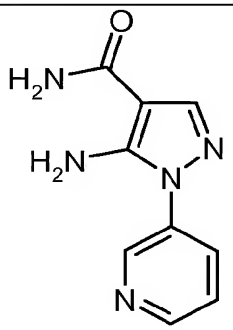
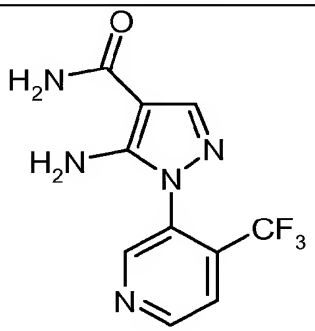
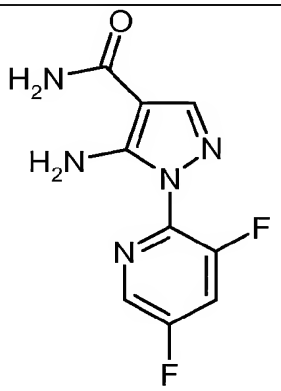


4.7 g of (23.13 mmol) of example 7B were dissolved in ethanol and then the temperature was lowered at 0°-5°C. A solution of 30% ammonium hydroxide (110 ml; 832 mmol) and 35% hydrogen peroxide (46 ml; 535 mmol) was then added drop wise. The reaction was heated to 20°C and the reaction mixture stirred for two additional hours. The formed precipitate was filtered and dried under vaccum. 4.4 g of the desired compound were obtained (19.89 mmol; yield = 86%).

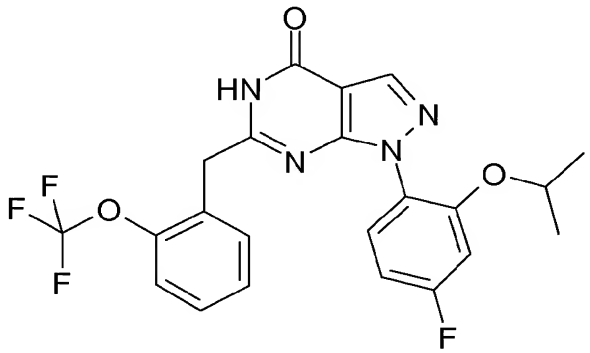
LC-MS ((Method Grad-C18-Acidic): RT = 0.6 min

MS (ESI pos): m/z = 222 (M+H)+

The following examples were synthesized in analogy to the preparation of example 9A, using the corresponding 5-amino-1H-pyrazole-4-carbonitriles as starting materials:

	structure	starting material	RT [min]	MS (m/z)
Example 9B		Example 7C	0.61 (Method Grad_C8_NH_4COOH)	204 $(M+H)^+$ ESI pos
Example 9C		Example 7A	3.72 (Method 1E)	272 $(M+H)^+$ APCI
Example 9D		Example 7D	1.69 ((Method Grad_C8__NH4COOH))	240 $(M+H)^+$ ESI

Example 10A



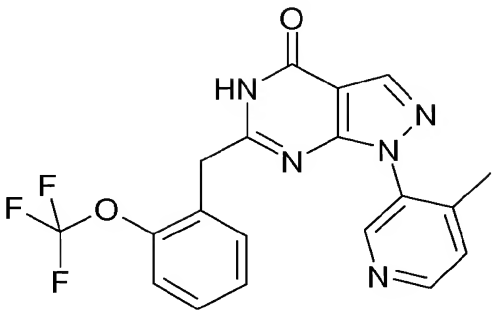
Example 10A was synthesized in analogy to example 3 using example 8V as starting material.

LC-MS (Method 1): RT = 1.68 min

MS (ESI pos): m/z = 463 (M+H)+

Exemplary embodiments:

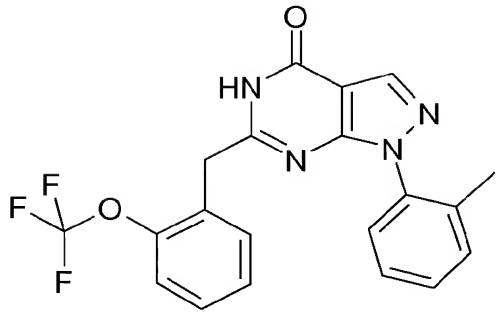
Example 1



0.080 g (0.37 mmol) of 5-amino-1-(4-methyl-pyridin-3-yl)-1H-pyrazole-4-carboxylic acid amide (compare WO 04-099211) were dissolved in 1.5 ml of absolute ethanol and 0.31 g (1.3 mmol) of example 1B and 0.059 g (1.5 mmol) of sodium hydride (60% suspension in mineral oil) were added. The reaction mixture was heated to reflux overnight. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. The remaining residue was treated with water (25 ml) and extracted three times with ethyl acetate. The organic layer was dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure. The remaining residue was purified by preparative HPLC (eluent A: water, eluent B: acetonitrile). 106 mg (72% of theory) of the product were obtained.

TLC (CH_2Cl_2/MeOH; 10:1): R_f = 0.44.

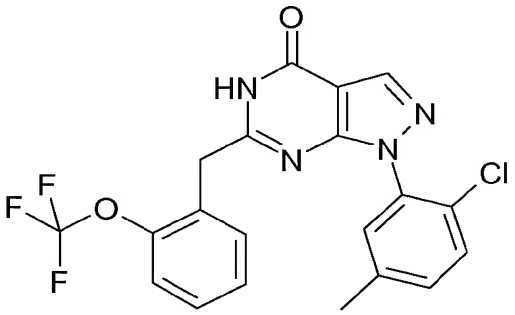
Example 2



In analogy to the preparation of example 1, 0.21 g (56% of theory) of the desired product were obtained from 0.20 g (0.92 mmol) of 5-amino-1-o-tolyl-1H-pyrazole-4-carboxylic acid amide (compare WO 04-099211) in 4.0 ml of absolute ethanol, 0.77 g (3.2 mmol) of example 1B, and 0.015 g (3.7 mmol) of sodium hydride (60% suspension in mineral oil).

TLC (CH_2Cl_2/MeOH; 10:1): R_f = 0.6.

Example 3

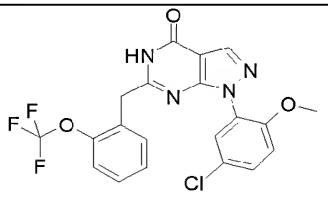
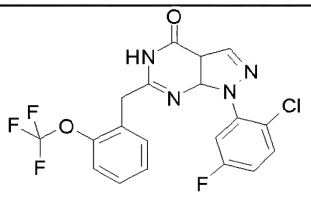
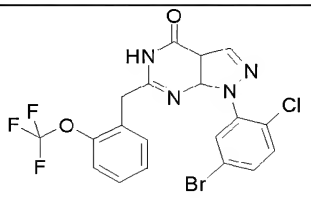
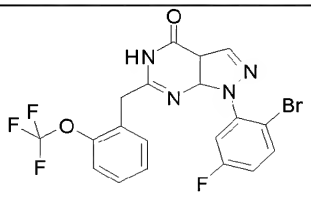
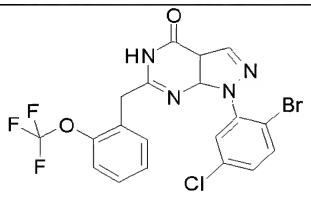
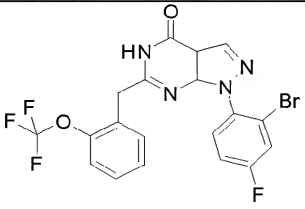


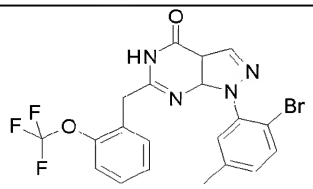
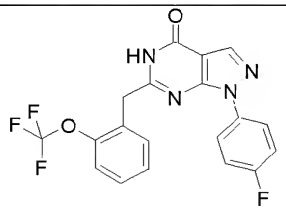
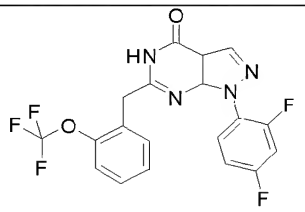
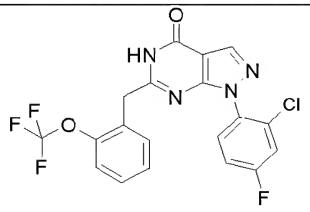
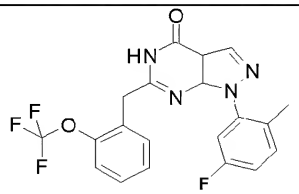
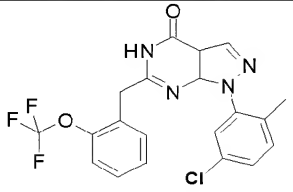
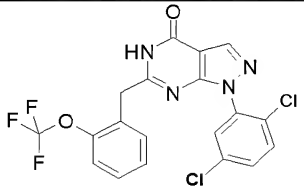
0.150 g (0.60 mmol) of example 8A were dissolved in 4.0 ml of absolute ethanol, 297 mg (1.20 mmol) of example 1A, and 71.8 mg (1.80 mmol) of sodium hydride (60% suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. The remaining residue was treated with water (10 ml) and extracted three times with ethyl acetate. The organic layer was dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure. The remaining residue was purified by preparative HPLC (eluent A: water + 0.13% TFA, eluent B: acetonitrile). 131 mg (50% of theory) of the product were obtained as a colourless solid.

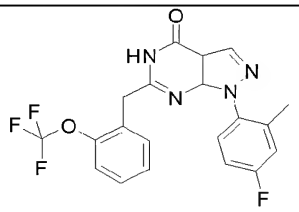
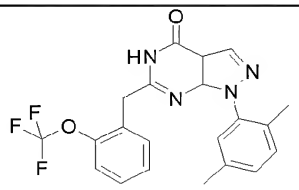
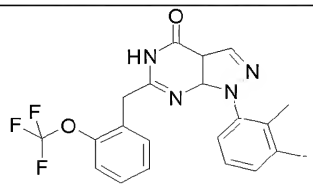
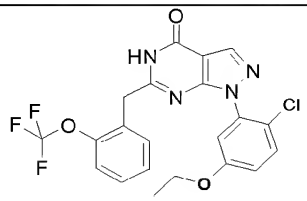
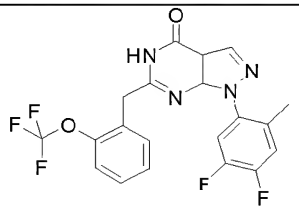
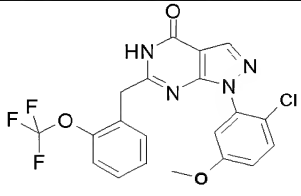
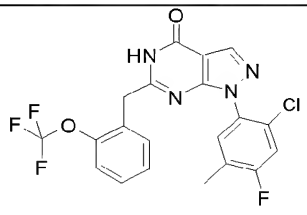
LC-MS (Method 1): RT = 1.64 min

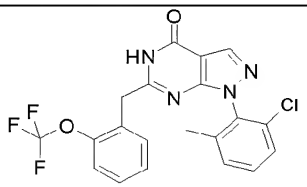
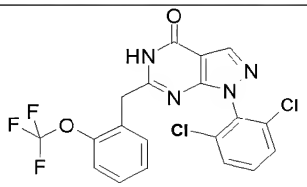
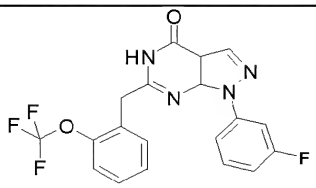
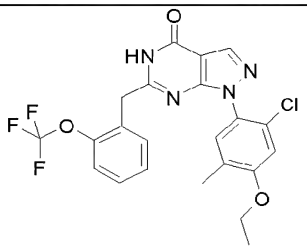
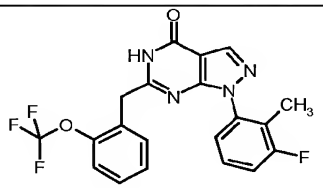
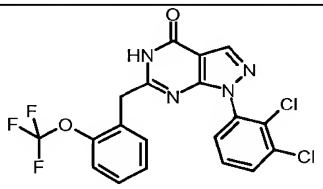
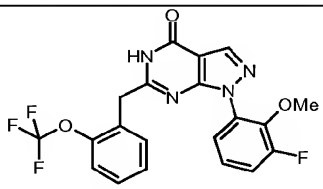
MS (ESI pos): m/z = 435/437 (Cl) $(M+H)^+$.

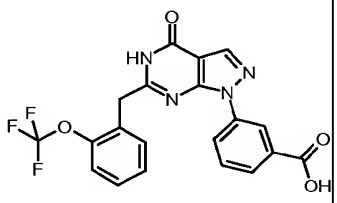
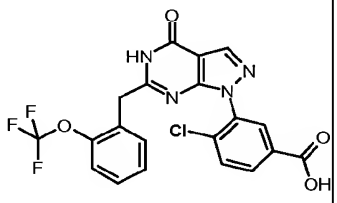
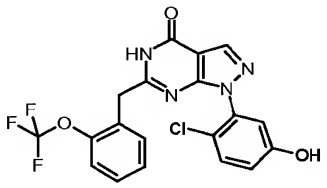
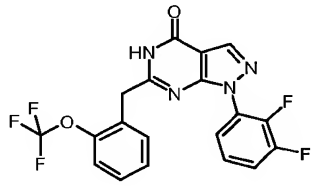
The following examples were synthesized in analogy to the preparation of example 3, using the corresponding 5-amino-1H-pyrazole-4-carboxylic acid amides as starting materials:

	structure	starting material	RT [min]	MS (ESI pos/neg, m/z)
Example 4		Example 8B	1.62 (Method 1)	451/453 (Cl) $(M+H)^+$
Example 5		Example 8C	1.60 (Method 1)	439/441 (Cl) $(M+H)^+$
Example 6		Example 8D	1.72 (Method 1)	499/501/503 (Br,Cl) $(M+H)^+$
Example 7		Example 8E	1.61 (Method 1)	483/485 (Br) $(M+H)^+$
Example 8		Example 8F	1.68 (Method 1)	499/501/503 (Br,Cl) $(M+H)^+$
Example 9		Example 8G	1.68 (Method 1)	483/485 (Br) $(M+H)^+$

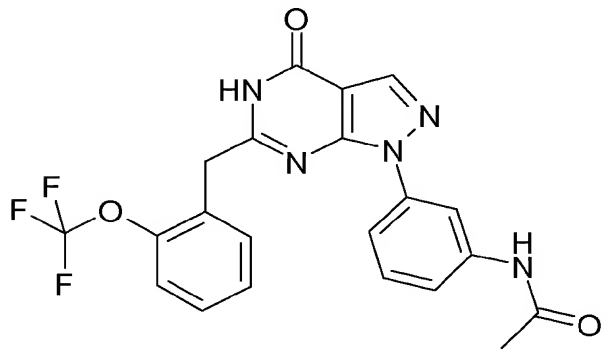
	structure	starting material	RT [min]	MS (ESI pos/neg, m/z)
Example 10		Example 8H	1.65 (Method 1)	479/481 (Br) $(M+H)^+$
Example 11		Example 8I	1.66 (Method 1)	405 $(M+H)^+$
Example 12		Example 8J	1.48 (Method 2)	423 $(M+H)^+$
Example 13		Example 8K	1.62 (Method 1)	439/441 (Cl) $(M+H)^+$
Example 14		Example 8L	1.64 (Method 1)	419 $(M+H)^+$
Example 15		Example 8M	1.72 (Method 1)	435/437 (Cl) $(M+H)^+$
Example 16		Example 8N	1.49 (Method 1)	455/457/459 (2Cl) $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos/neg, m/z)
Example 17		Example 8O	1.61 (Method 1)	419 $(M+H)^+$
Example 18		Example 8P	1.68 (Method 1)	415 $(M+H)^+$
Example 19		Example 8Q	1.65 (Method 1)	415 $(M+H)^+$
Example 20		Example 8R	1.68 (Method 1)	465/467 (Cl) $(M+H)^+$
Example 21		Example 8S	1.67 (Method 1)	437 $(M+H)^+$
Example 22		Example 8T	1.59 (Method 1)	451/453 (Cl) $(M+H)^+$
Example 23		Example 8U	1.70 (Method 1)	453/455 (Cl) $(M+H)^+$

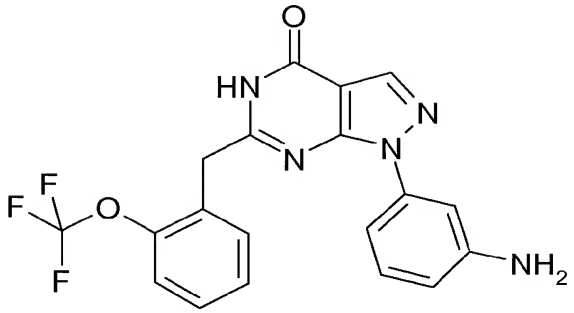
	structure	starting material	RT [min]	MS (ESI pos/neg, m/z)
Example 24		Example 8W	1.63 (Method 1)	435/437 (Cl) $(M+H)^+$
Example 25		Example 8X	1.61 (Method 1)	455/457/459 (2Cl) $(M+H)^+$
Example 26		Example 8Y	1.70 (Method 1)	405 $(M+H)^+$
Example 27		Example 8Z	1.77 (Method 1)	479/481 (Cl) $(M+H)^+$
Example 28		Example 8AA	1.70 (Method 1)	419 (Cl) $(M+H)^+$
Example 29		Example 8AB	1.60 (Method 1)	453/456 (2Cl) $(M-H)^+$
Example 30		Example 8AC	1.57 (Method 1)	435 $(M+H)^+$

	structure	starting material	RT [min]	MS (ESI pos/neg, m/z)
Example 30-1		Example 8 AG	1.39 (Method 1)	431 $(M)^+$
Example 30-2		Example 8 AF	1.39 (Method 1)	463/465 (Cl) $(M-H)^-$)
Example 30-3		Example 8 AH	1.41 (Method 1)	435/437 (Cl) $(M-H)^-$)
Example 30-4			1.53 (Method 1)	423 $(M+H)^+$

Example 30-5



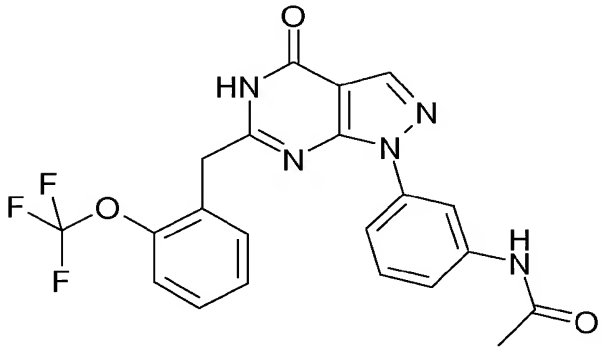
a)



The precursor to example 30-5 was synthesized in analogy to the preparation of example 3, using example 8AI as starting material.

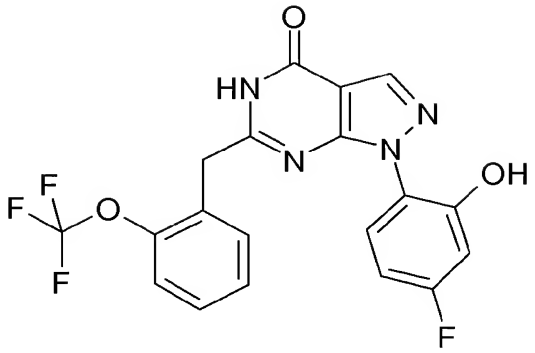
LC-MS (Method 1): RT = 1.23 min
MS (ESI pos): m/z = 402 (M+H)+.

b)



0.10 g (0.20 mmol) of a) were dissolved in 5.0 ml of dichloromethane and 55.5 µL (0.40 mmol) triethylamine were added. The mixture was stirred at room temperature for 5 min followed by the addition of 29,9 µL (0.40 mmol) acetylchloride and further stirring at room temperature for 12 h. The reaction mixture was evaporated to dryness. Water was added and the resulting precipitate was filtered off and dried to afford 76.1 mg (86%) of example 30-4.
LC-MS (Method 1): RT = 1.36 min
MS (ESI pos): m/z = 444 (M+H)+.

Example 31

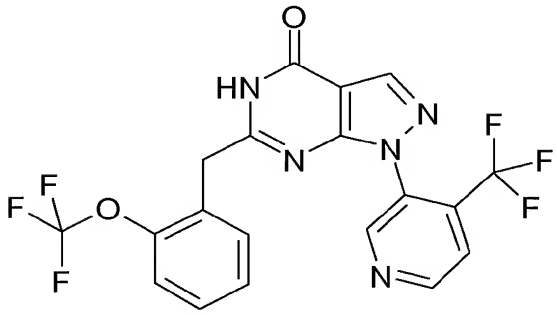


0.02 g (0.043 mmol) of example 10A were dissolved in 1.0 ml of BBr_3 and stirred at room temperature for 2 h. Water was added and the resulting slurry extracted with dichloromethane. The organic phase was separated, dried and evaporated to dryness to yield 18.2 mg (54% of theory) of the product as a colourless solid.

LC-MS (Method 1): RT = 1.55 min

MS (ESI pos): m/z = 421 $(M+H)^+$

Example 32



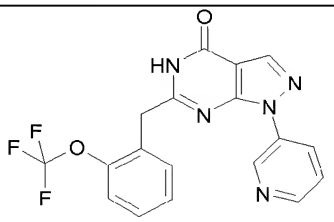
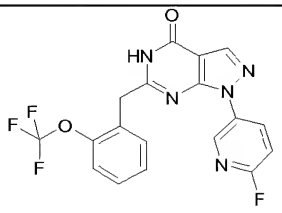
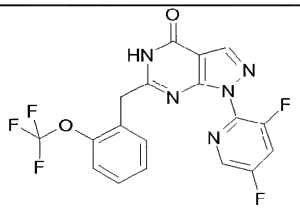
Example 9C (0.15g; 0.65 mmol) was suspended in a 50 ml flask with polyphosphoric acid (1g) and 2-(trifluoromethoxy)phenylacetic acid (428 mg; 1.94 mmol). The mixture, under mechanic stirring, was heated at 120°C during 24 hours and the temperature was then lowered at room temperature, water was added (10 ml) and pH value was adjusted to 7 by addition of NH_4OH (30% solution). The aqueous phase was extracted with CH_2Cl_2 (2x20ml) and the organic phase was dried over sodium sulphate. The crude product was purified by flash chromatography. Eluent: hexane/ethyl acetate 30/70.

Obtained 40mg (0.09 mmol; yield = 34%) of the desired compound

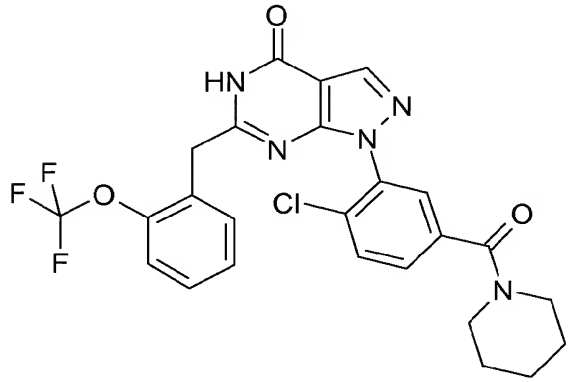
LC-MS (Method 1E): RT = 8.35 min

MS (APCI): m/z = 456 (M+H)

The following examples were synthesized in analogy to the preparation of example 32, using the corresponding 5-amino-1H-pyrazole-4-carboxylic acid amides as starting materials:

	structure	starting material	RT [min]	MS (APCI, m/z)
Example 33		Example 9B	7.35 (Method 1E)	388 $(M+H)^+$
Example 34		Example 9A	6.93 (Method 1D)	406 $(M+H)^+$
Example 39		Example 9D	11,59 (Method 2F)	424 $(M+H)^+$

Example 35

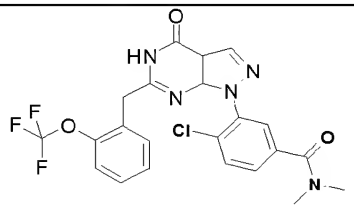
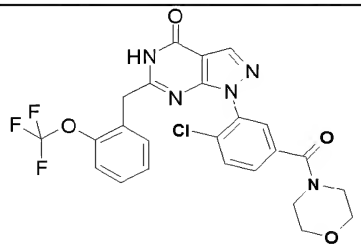
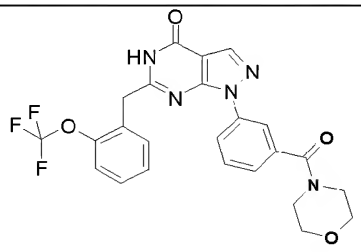


0.05 g (0.11 mmol) of example 30-2, 11.0 µL piperidine (0.11 mmol), 40.0 mg TBTU (0.13 mmol) and 40.0 µL DIPEA (0.23 mmol) were dissolved in 5 mL dichloromethane and stirred at room temperature over night. Standard aqueous work up and HPLC-separation (eluent A: water + 0.13% TFA, eluent B: acetonitrile) afforded 35 mg (61%) of example 35.

LC-MS (Method 1): RT = 1.54 min

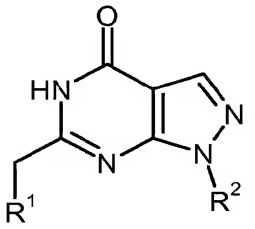
MS (ESI pos): m/z = 532/534 (Cl) (M+H)+

The following examples were synthesized in analogy to the preparation of example 35, using the corresponding amines:

	structure	starting material	RT [min]	MS (ESI pos, m/z)
Example 36		Example 30-2	1.38 (Method 1)	492/494 (Cl) $(M+H)^+$
Example 37		Example 30-2	1.37 (Method 1)	534/536 (Cl) $(M+H)^+$
Example 38		Example 30-1	1.37 (Method 1)	500 $(M+H)^+$

CLAIMS

1. A compound according to claim 1, characterised by general formula I:



(I),

with

R^1

being phenyl or pyridyl, any of which is substituted with 1 to 4, preferably 1 to 3 substituents X ;

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6-alkylamino, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_6-C_{10}-aryl-carbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by 1 to 3 radicals independently of one another selected from the group of hydroxy, cyano, halogen, hydroxy-carbonyl and a group of the formula $-NR^3R^4$,

X

independently of each other being selected from C_2-C_6-alkyl or C_1-C_6-alkoxy, where C_2-C_6-alkyl and C_1-C_6-alkoxy are at least dihalogenated up to perhalogenated, preferably with 2 to 6 halogen substituents, and the halogen

atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro, whereby at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferably at least twofold halogenated;

R^2

being phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6-alkylamino, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, hydroxycarbonyl and a group of the formula $-NR^3R^4$,

R^3

being hydrogen or C_1-C_6-alkyl,

and R^4

being hydrogen or C_1-C_6-alkyl,

or R^3 and R^4 together with the nitrogen atom to which they are bonded are 5- to 8-membered heterocyclyl.

2. A compound according to claim 1, characterized in that

R^1

being phenyl or pyridyl, any of which is substituted with 1 to 3 substituents X ;

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, cyano, trifluoromethyl, nitro, halogen, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_6-C_{10}-arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylcarbonylamino, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, and a group of the formula – NR^3R^4,

X

independently of each other being selected from C_2-C_6-alkyl or C_1-C_6-alkoxy, where C_2-C_6-alkyl and C_1-C_6-alkoxy are at least dihalogenated up to perhalogenated, preferably with 2 to 6 halogen substituents, and the halogen atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro, whereby at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferably at least twofold halogenated;

R^2

being phenyl or heteroaryl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-

alkoxy, hydroxycarbonyl, cyano, trifluoromethyl, amino, nitro, hydroxy, C_1-C_6-alkylamino, halogen, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_6-C_{10}-arylcarbonylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkylsulphonylamino, C_1-C_6-alkylsulphonyl and C_1-C_6-alkylthio are optionally substituted by one to three radicals independently of one another selected from the group of hydroxy, cyano, halogen, and a group of the formula –NR^3R^4,

and the remaining characteristics as defined in claim 1.

3. A compound according to claim 1, characterized in that

R^1

being phenyl or pyridyl, any of which is substituted with one to three substituents X;

and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, trifluoromethyl, halogen,

X

independently of each other being selected from C_2-C_6-alkyl or C_1-C_6-alkoxy, where C_2-C_6-alkyl and C_1-C_6-alkoxy are at least dihalogenated up to perhalogenated, preferably with 2 to 6 halogen substituents, and the halogen atoms being selected from the group of fluoro, chloro and bromo, preferably fluoro, whereby at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferably at least twofold halogenated;

R^2

being phenyl or pyridyl, where phenyl is substituted by 1 to 3 radicals and heteroaryl is optionally substituted by 1 to 3 radicals in each case independently of one another selected from the group of C_1-C_6-alkyl, C_1-C_6-alkoxy, trifluoromethyl, halogen and C_1-C_6-alkylthio,

where each of C_1-C_6-alkyl, C_1-C_6-alkoxy and C_1-C_6-alkylthio, are optionally substituted by one to three halogen radicals,

and the remaining characteristics as defined in claim 1.

4. A compound according to any of claims 1 to 3, characterized in that R^1 being phenyl or pyridyl, any of which being substituted with 1 to 3 X whereas X being C_2-C_6-alkyl, preferably C_2-alkyl , with the further optional substitution pattern for C_2-C_6-alkyl and/or phenyl or C_2-C_6-alkyl and/or pyridyl and the remaining features as defined in any of these claims 1 to 3.

5. A compound according to any of claims 1 to 2, characterized in that in R^1 being phenyl or pyridyl, any of which being substituted with 1 to 3 X, whereas X being C_1-C_6-alkoxy, preferably C_1-alkoxy with the further optional substitution pattern for C_1-C_6-alkoxy and/or phenyl or C_1-C_6-alkoxy and/or pyridyl and the remaining features as defined in any of these claims 1 to 2.

6. A compound according to any of claims 1 to 3 or 5, characterized in that

R^1

being phenyl or pyridyl, any of which being substituted with 1 to 3 X, whereas X being C_1-C_6-alkoxy, substituted by at least 2, preferably 2 to 6 halogen atoms, selected from the group of fluoro, chloro and bromo, preferably fluoro substitutents, whereby preferably at least the C-atom which constitutes the

beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferred at least twofold halogenated;

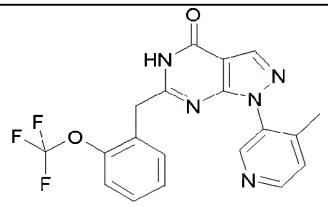
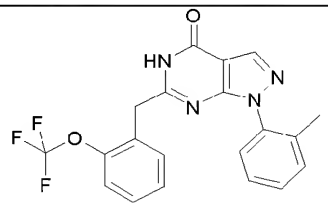
and with the option that each of phenyl or pyridyl in addition may be substituted by up to 3 radicals independently of one another selected from the group of C_1-C_6-alkyl, trifluoromethyl, halogen,

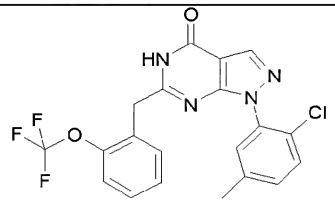
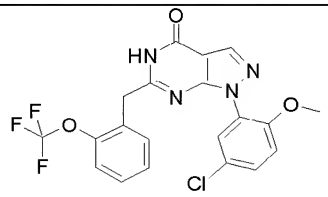
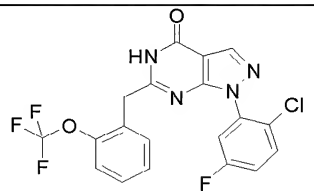
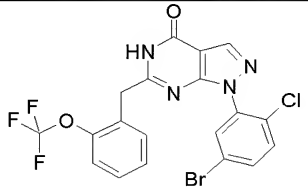
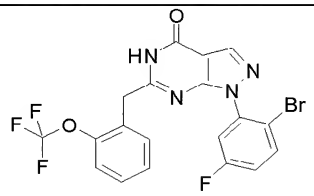
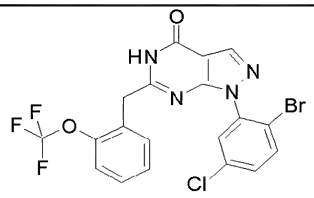
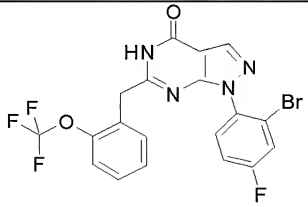
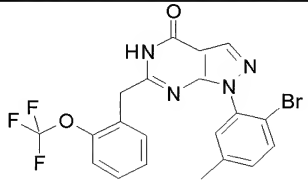
and the remaining characteristics as defined in claim 1.

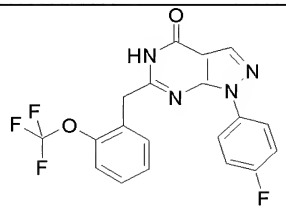
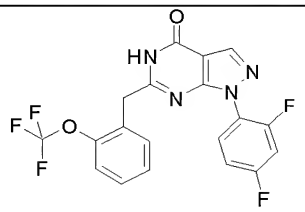
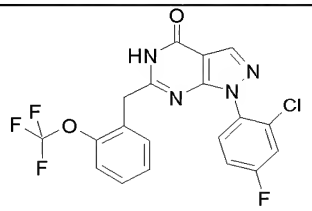
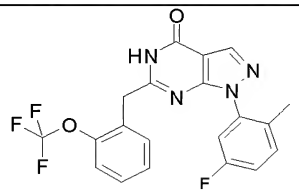
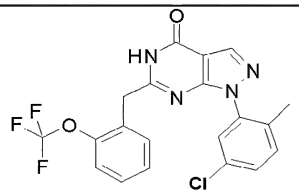
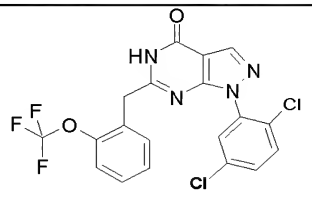
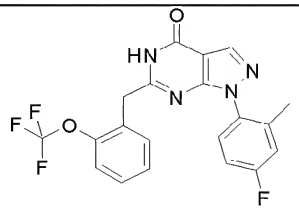
7. A compound according to any of claims 1 to 6, characterized in that for R^1 the substitution pattern at the one to 3 mandatory substituents X are at least 2, more preferably 3 fluoro substituents, whereby preferably at least the C-atom which constitutes the beta position with respect to the link to the phenyl or pyridyl is at least one fold or more preferred at least twofold halogenated.

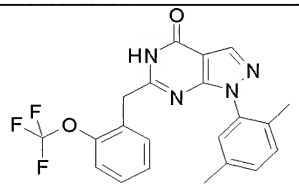
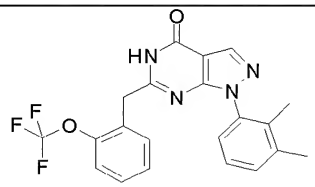
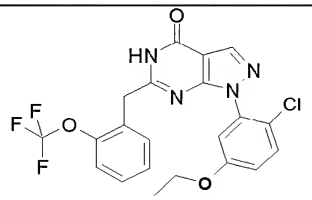
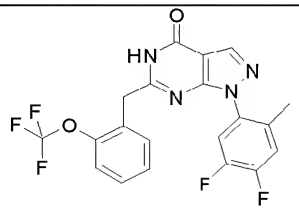
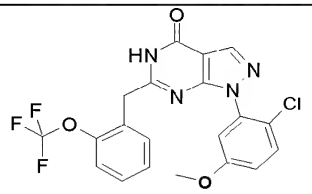
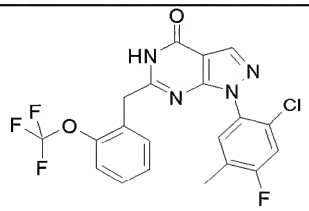
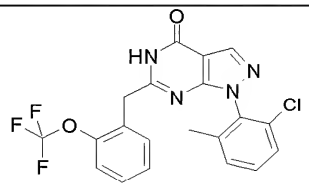
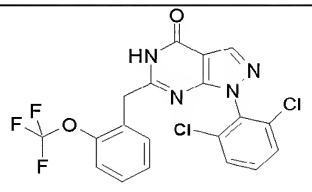
8. A compound according to any of claims 1 to 7, characterized in that R^1 is phenyl substituted as defined in any of claims 1 to 5, preferably 2-trifluoromethoxyphenyl .

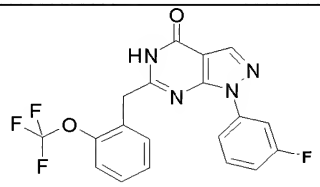
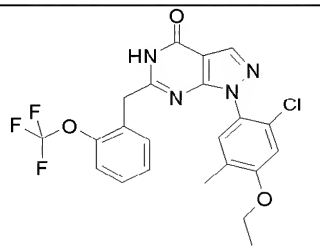
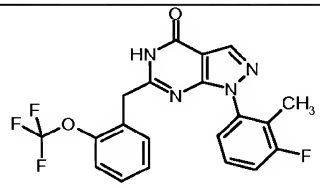
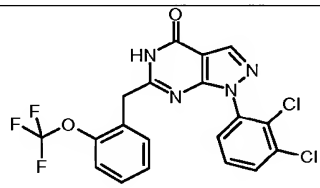
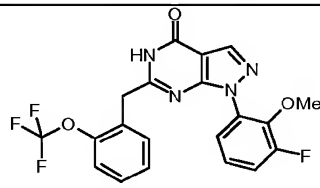
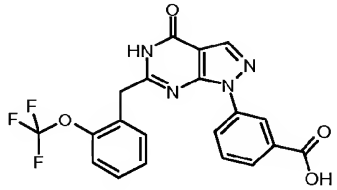
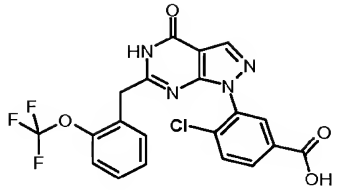
9. A compound according to claim 1 that is each one of

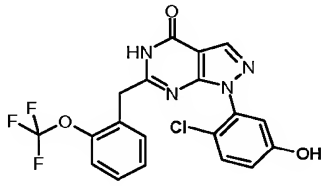
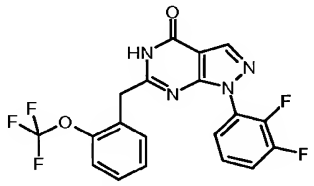
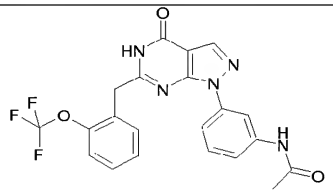
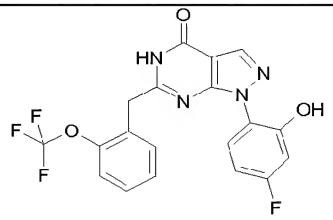
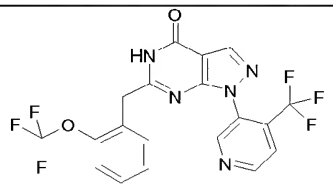
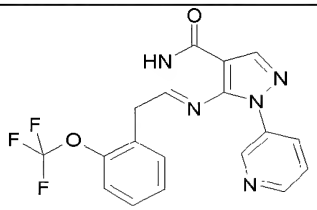
Compound No.	Structure
1	
2	

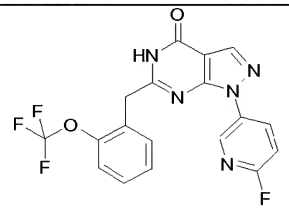
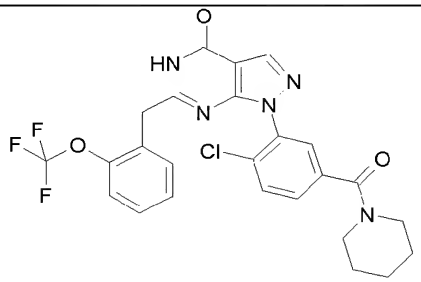
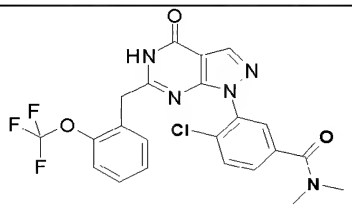
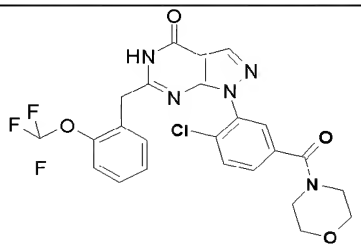
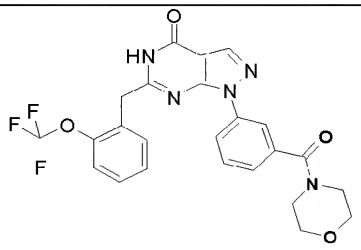
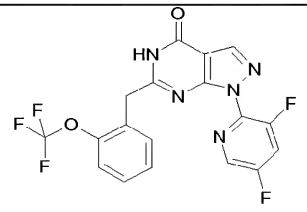
3	
4	
5	
6	
7	
8	
9	
10	

11	
12	
13	
14	
15	
16	
17	

18	
19	
20	
21	
22	
23	
24	
25	

26	
27	
28	
29	
30	
30-1	
30-2	

30-3	
30-4	
30-5	
31	
32	
33	

34	
35	
36	
37	
38	
39	

10. A pharmaceutically acceptable salt of a compound according to any of the preceeding claims.

11. Use of a compound according to any of claims 1 to 9 for the manufacture of medicament for the treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory, preferably for the treatment, amelioration and / or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

12. Use of a compound according to any of claims 1 to 9 for the manufacture of medicament for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetis mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

13. Use of a compound according to any of claims 1 to 9 for the manufacture of medicament for the treatment, amelioration and / or prevention, preferably the

treatment, of a disease, the course of which can be influenced by the inhibition of PDE9.

14. Use of a compound according to any of claims 1 to 9 in combination with another therapeutically effective compound, preferably selected from the group of beta-secretase inhibitors; gamma-secretase inhibitors; amyloid aggregation inhibitors; directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants; anti-inflammatory substances; HMG-CoA reductase inhibitors, statins; acetylcholinesterase inhibitors, NMDA receptor antagonists; AMPA receptor agonists; AMPA receptor positive modulators, AMPkines, monoamine receptor reuptake inhibitors, substances modulating the concentration or release of neurotransmitters; substances modulating the secretion of growth hormone; CB-1 receptor antagonists or inverse agonists; antibiotics; PDE2, PDE4, PDE5, PDE10 inhibitors, GABAA receptor inverse agonists, GABAA receptor antagonists, nicotinic receptor agonists or partial agonists or positive modulators, alpha4beta2 nicotinic receptor agonists or partial agonists or positive modulators, alpha7 nicotinic receptor agonists or partial agonists or positive modulators; histamine H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, alpha2-adrenoreceptor antagonists, calcium antagonists, muscarinic receptor M1 agonists or partial agonists or positive modulators, muscarinic receptor M2 antagonists, muscarinic receptor M4 antagonists, metabotropic glutamate-receptor 5 positive modulators, and / or other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced for the preparation of a medication for the treatment of a disease as defined in any of claims 11 to 13.

15. Pharmaceutical composition comprising a compound according to any of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/066350

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/099210 A (BAYER HEALTHCARE AG [DE]; HENDRIX MARTIN [DE]; BAERFACKER LARS [DE]; E) 18 November 2004 (2004-11-18) cited in the application the whole document	1-15
Y	WO 2004/018474 A (BAYER HEALTHCARE AG [DE]; HENDRIX MARTIN [DE]; BOESS FRANK-GERHARD [DE] 4 March 2004 (2004-03-04) the whole document	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 2009	04/03/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fink, Dieter

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/066350

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